

ACTA PÆDIATRICA

EDITORES:

A. LICHTENSTEIN, STOCKHOLM, A. WALLGREN, STOCKHOLM

REDACTORES:

IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KØBENHAVN, C. E. BLOCH, KØBENHAVN, P. PLUM, KØBENHAVN. *IN FENNIA:* P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C.-E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. *IN HOLLANDIA:* E. GORTER, LEIDEN, CORNELIA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. *IN NORVEGIA:* LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIM TOVERUD, OSLO. *IN SUECIA:* C. GYLLENSWÄRD, UPPSALA, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, WILHELM WERNSTEDT, STOCKHOLM, Y. ÅKERRÉN, GÖTEBORG.

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A. LICHTENSTEIN

KRONPRINSESSAN LOVISAS BARNSJUKHUS.

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ACTA PÆDIATRICA



HR

FROM THE SACHS' CHILDREN'S HOSPITAL, STOCKHOLM. (FORMER
HEAD: PROFESSOR C. GYLLENSWÄRD. PRESENT HEAD: DOCENT J.
HENNING MAGNUSSON.)

A Comparison Between the Sedimentation Rates of Children in Day-Nurseries and Children Cared for in Their Homes.

By

ERIK FRISSELL.

Day care institutions for children are at present the subject of deep and justified interest. A public committee, »The national committee of day care institutions», is at present engaged in planning their future organization, laying stress first of all on what should be done to the obvious medical drawbacks in the present set-up. The following report may help make clear the medical problems connected with child care in day-nurseries. The investigation was already made in 1943 on the initiative of Prof. C. GYLLENSWÄRD but has not been published before.

The investigation is based on the following supposition. According to modern ideas, a large group of the common infections of the upper respiratory tract is caused by viruses. In a large number of cases, these virus infections are often closely followed by a bacterial infection (causing purulent catarrh, otitis, sinusitis etc.) with regular increase of the sedimentation rate (S. R.). In a day-nursery with its many chances for cross-infections, the children scarcely have time to recover from one infection before succumbing to the next. In other words, the essential conditions exist for the development of S. R.-increasing complications which heal very slowly and only with difficulty due to the perpetual source of contagion. Many of the children therefore permanently go about with more or less latent infections with a probable S. R. increase.

(Submitted for publication April 26, 1946.)

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In order to find out between which ages this condition prevails and to draw a comparison between day-nursery children and children who remain in and about their homes without the same risk for cross-infections, the sedimentation rate was determined on all children in three Stockholm day-nurseries from September to November 1943 (i. e. the North and West Katarina day-nurseries in the district called »Södermalm» and the Een Foundation day-nursery on »Kungsholmen»). As comparative material, those children were chosen who, during these same months, visited child care centers in the neighbourhood of the two Katarina day-nurseries and in Matteus' parish.

Approximately 100 children are taken charge of daily at the North Katarina day-nursery, though the nursery was originally built for only 83 children. Eight infants are cared for on the top floor in a medium-sized room situated immediately within a day room for twenty 1—2 year olds. This latter group has also a sleeping room on the top floor. These two groups are separated only by a door which is kept closed. 40 children from 2—5 years old, have 2 day- and 1 sleeping room on the middle floor. On the bottom floor, there are 2 rooms for 35 children from 5—7 years. The same stairs are used by all. The playground outdoors is often windy.

The Western Katarina day-nursery takes care of approximately 95—100 children daily, though it was only meant to accomodate 90 at the outside. On the top storey, 11 infants are cared for in 2 rather small rooms with glass partitions in between the rooms. Twenty-five 1—3 year olds dispose of 2 day- and 1 dining room on the same floor. The same hall is used by all, causing infections to spread easily from one group to another. Fifty-one children from 3—7 years have 4 medium-sized rooms on the bottom floor. The same entrance is for all age groups. There is a playground outside.

The Een Foundation home for unmarried mothers with children, runs a day-nursery with accomodations for 50 children on the fifth floor. The two age groups 1½—4 years and 4—7 years, both consisting of 20 children, have each the use of 2 large rooms situated at the opposite ends of a long cloak room. The infant ward with 8 beds, is completely isolated on a floor by itself. There is a large playground on the house roof for all children. This day-nursery is one of the best equipped in Stockholm from the point of view of isolation, personnel and management.

All blood samples were taken and set up by the author. Only in a few cases were experienced nurses allowed to read them

off. Ström's micro-method (*Acta Pæd.*, 14, 567, 1933) was used for the sedimentation rates. Reading was done after one half and one hour periods, but only the 1 hour values were included in the statistical calculations. All cases in which the $\frac{1}{2}$ and 1 hour values did not seem to be reasonably in proportion to each other, were rejected.

The sedimentation rate was determined twice on the day-nursery children with an interval of 3—4 weeks. Children from whom only one value could be obtained, were excluded from the calculations. The final group consisted of 196 children from 0—7 years of age. The S. R. values were grouped under the headings, «Day-nursery, first series» and the second lot, «Day-nursery, second series». Both groups were treated absolutely separately and both consisted of the same 196 children.

The comparative material was made up of 266 children from different child care centers. The children belonged to the same age group, i. e. 0—7 years, and the tests were made during the same months i. e. between Sept.—Nov. 1943. These children were called «controls». For practical reasons, the sedimentation rates could only be determined once on this group. The same series of controls is therefore used in the comparisons with the two lots of day-nursery children. Due to the fact that the children belonging to the older age groups only rarely visited the child care centers at the time of this examination, the older group is somewhat misrepresented in comparison to the younger. None of the controls had ever visited any day-nursery. Three of the 4—6 year olds were in kindergarten two hours daily.

After determining the means and standard errors of the S. R. of the different age groups, it became evident that the relatively small number of children in the different age categories made a statistical study somewhat uncertain. Furthermore, 3.0 years seemed to be the upper limit for those age groups within which a significant difference in the S. R. of day-nursery children and controls could be proved. The author therefore chose to work with only 2 age-groups: 0—2.9 years and 3.0—7 years.

The following table shows how the material was put together.

Table 1.

| | | S. R. in millimeters | | | | | |
|-------------|-------------------------|----------------------|-------|-------|-------|-------|-------|
| | | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 |
| 0-2.9 years | Controls | 59 | 109 | 40 | 8 | 4 | |
| | Day-nursery, 1st series | 7 | 25 | 24 | 16 | 8 | 1 |
| | » 2nd » | 8 | 32 | 20 | 10 | 8 | 3 |
| 3,0-7 years | Controls | 13 | 21 | 6 | 3 | 1 | |
| | Day-nursery, 1st series | 24 | 46 | 35 | 6 | 2 | 2 |
| | » 2nd » | 27 | 54 | 27 | 7 | | |

Graphically, the material appears as follows. (The sedimentation rate is registered in millimeters on the x-axis, and the number of children is expressed as a percent of each group on the y-axis.)

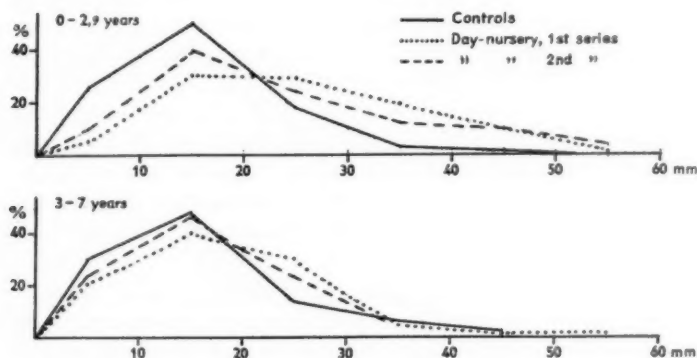


Fig. 1.

The curves of the age group 0-2.9 years, show a distinct difference between the controls and the two lots of day-nursery children. The curves of the latter group are flatter and more drawn-out to the right, i. e. the individuals shift from lower to

higher S. R. values. The same tendency is still evident, though not significant, within the age group above 3.0 years.

Table 2 shows the numerical values of the mean S. R. and its standard errors expressed in millimeters, as well as the dispersion and its standard errors for the different groups of children.

Table 2.

| | 0—2.9 years | | | 3.0—7 years | | |
|-------------------------|---------------|---------------------------|---------------------------|---------------|---------------------------|---------------------------|
| | Con- trols | Day-nursery 1st series | Day-nursery 2nd series | Con- trols | Day-nursery 1st series | Day-nursery 2nd series |
| <i>N</i> | 220 | 81 | 81 | 44 | 115 | 115 |
| <i>M</i> | 14.9 | 24.0 | 23.7 | 15.0 | 17.7 | 15.7 |
| $\varepsilon(M)$ | 0.6 | 1.3 | 1.4 | 1.4 | 0.9 | 0.7 |
| σ^1 | 8.2 | 11.3 | 12.4 | 9.1 | 9.8 | 7.8 |
| $\varepsilon(\sigma)^2$ | 0.6 | 1.1 | 1.3 | 1.4 | 0.9 | 0.7 |

This table shows a clear, statistically confirmed difference in the age group 0—2.9 years between the sedimentation rates of the day-nursery children and the controls, both as to the means and dispersion.

Difference in means (day-nursery children, 2nd series: controls) = 8.8 ± 1.52 mm.

Difference in dispersion (day-nursery children, second series: controls) = 4.2 ± 1.43 mm.

The figures back up the graphs in proving the difference in dispersion for the age group 0—2.9 years. The graphs show the sedimentation rates in the control children's curve to be more spread out.

¹ σ^2 has been corrected by Sheppard's formula $-\frac{\omega^2}{12} = -8.3$ (class interval $\omega = 10$).

² Calculated according to the formula $\varepsilon(\sigma) = \frac{\sqrt{\mu_4 - \sigma^4}}{2\sigma\sqrt{N}}$, which for a

Pearson III curve was reduced to $\varepsilon(\sigma) = \frac{\sigma\sqrt{1 + \frac{3\sigma}{M^2}}}{\sqrt{2N}}$. The constant σ and M were determined from the material.

No similar, significant differences within the age group 3.0—7 years are to be found. If the younger and older age groups of day-nursery children are compared, however, a difference in means is evident. A corresponding difference is also found in the illness frequency of different ages of day-nursery children as reflected in the admission figures of the children's hospitals. During the three months this investigation was being carried on (Sept.—Nov. 1943), altogether 19 day-nursery children were admitted to the Sachs' Children's Hospital. 8 of these were between 0—2 years, 7 from 2—3 years, and 4 from 3—7 years of age.

In order to illustrate this problem even better from a statistical point of view, the material was referred to Docent G. ELFVING, temporary professor of the University College, Stockholm. After checking and revising, he stated as follows.

As the present curves are obviously not of the normal type, it has been interesting to find a theoretical distribution which could accurately describe the empiric material. After several different trials, type III of the so-called Pearson curve furnished good results. The frequency function for this distribution is shown by the formula $f(x) = \frac{a^\lambda}{\Gamma(\lambda)} \cdot x^{\lambda-1} \cdot e^{-ax}$. For the constant values a and λ , which naturally vary from group to group, the values $\lambda = \frac{m^2}{G^2}$, $a = \frac{M}{G^2}$ are obtained according to the moment method. The conformity between the empiric and theoretic distribution was tested by the χ^2 -method in two cases (day-nursery children, 1st series 0—2.9 years, controls 0—2.9 years) and found to be very good.

A concrete idea of the variations in the distribution of the sedimentation rates is given by the so-called upper quartiles, i. e. those S. R. values exceeded by 25 % of the individuals of the group concerned. This value, worked out from theoretic distribution, is 19.4 mm for the controls, 0—2.9 years old, and 30.6 mm for day-nursery children the same age (first round).

The most outstanding differences in living conditions in the children's homes have been compared in table 3. The children

from the Een Foundation day-nursery have not been included, as the conditions there are very special. Only very reliable information has been included. The living conditions of the day-nursery children are, as expected, far worse than those of the controls. Their homes are generally smaller. This is partially compensated from the point of view of contagion by a greater number of brothers and sisters among the controls than among the day-nursery children, an important fact as to the development of cross-infections.

Table 3. Social conditions.

The numbers give the percents of day-nursery children (149) and controls (204) of whom information was included. The figures of the controls are within parentheses.

| | One room (with or without kitchenette) | | Two rooms (1 room and kitchen 2 rooms and kitchenette) | | | Three or more rooms (2 or more rooms and kitchen) | | | Mother unmarried, divorced or widow |
|-------|--|------------|--|--------------|------------|---|---------------|--------------|-------------------------------------|
| | 1 child | 2 children | 1 child | 2 children | 3 children | 1 child | 2 children | 3 children | |
| 0—2.9 | 8 (4) | 1 (—) | 27 (30) | 6 (9) | 0.5 (1) | 5 (20) | 0.5 (8) | — (7) | 11 (1) |
| 3.0—7 | 8 (—) | 2 (—) | 20 (6) | 9.5 (4) | 2 (—) | 3 (2) | 7 (6.5) | 0.5 (2.5) | 14 (0.5) |
| Total | 16 (4) | 3 (—) | 47 (36) | 15.5 (13) | 2.5 (1) | 8 (22) | 7.5 (14.5) | 0.5 (9.5) | 25 (1.5) |

Summary.

During a sedimentation rate investigation made from Sept.—Nov. 1943 in Stockholm on 196 day-nursery children and 266 children cared for in their homes (controls), much higher rates were found among the day-nursery children than among the controls within the age group 0—2.9 years. The difference is significant, statistically.

A similar difference was also found to exist among the day-nursery children between the ages of 0—2.9 and 3.0—7 years, with higher rates for the younger group. The illness frequency in this group was also found to be greater. Out of 19 day-nursery children admitted to the Sachs' Children's Hospital during the months of this investigation, 15 children were under 3 years, and 4 between 3—7 years of age.

Résumé.

Au cours d'un examen, fait à Stockholm entre septembre et novembre 1943, de la sédimentation chez 196 enfants d'une crèche et chez 266 enfants soignés à leurs domiciles (contrôles) on a trouvé une sédimentation beaucoup plus forte chez les enfants de la crèche que parmi les contrôles dans le groupe des enfants de 0—2.9 ans. La différence est statistiquement significative.

Une différence similaire a été constatée aussi parmi les enfants d'une crèche entre les enfants de 0—2.9 ans et ceux de 3.0—7 ans, la sédimentation chez le groupe plus jeune étant plus élevée. La fréquence de maladies était aussi plus grande dans ce groupe. De 19 enfants d'une crèche admis à l'Hôpital d'enfants Sachs pendant les mois de l'observation, 15 avaient moins de 3 ans et 4 entre 3—7 ans.

Zusammenfassung.

Bei einer von Sept.—Nov. 1943 in Stockholm bei 196 Tagesheim-Kindern und 266 zuhause gepflegten Kindern (Kontrollen) vorgenommenen Untersuchung der Senkungsgeschwindigkeit ergab sich innerhalb der Altersgruppe 0—2.9 Jahre bei den Tagesheim-Kindern ein viel höherer Wert als bei den Kontrollkindern. Dieser Unterschied ist statistisch wertvoll.

Von den Tagesheim-Kindern zeigte die jüngere Gruppe höhere Senkungswerte und häufigere Erkrankungsfälle als die ältere.

Resumen.

En una investigación que se llevó a cabo desde septiembre de 1943 hasta noviembre del mismo año, en Estocolmo, sobre

la proporción de sedimentación de 196 niños atendidos en una guardería infantil y de otros 266 niños atendidos en sus respectivas casas (bajo control), se encontró que la proporción era mayor entre los niños de la guardería infantil que entre los que habían sido atendidos bajo control en sus casas en la edad de 0—2.9 años. Desde el punto de vista estadístico esta diferencia es significativa.

Se encontró que había una diferencia similar en los niños de la guardería infantil entre los grupos de 0 a 2.9 y 3.0 a 7 años de edad, respectivamente; la proporción era mayor en el grupo más joven. Se constató que también la frecuencia de enfermedades era mayor en este grupo. De un total de 19 niños de guarderías infantiles ingresados en el Hospital Infantil Sachs durante los meses en que se llevó a cabo la investigación, 15 tenían menos de tres años y los otros cuatro oscilaban entre tres y siete años.

(FROM THE WILHELMINA CHILDREN'S HOSPITAL, UTRECHT, DIRECTOR:
PROF. DR. A. TEN BOKKEL HUININK.)

Infantile Cortical Hyperostoses.

By

Dr. W. van ZEBEN.

CAFFEY (1) was the first (1939) to describe the case of a patient with scattered cortical thickenings in several bones. In all similar cases (2, 3) observed by him since — 10 in all up to now — the same morbid condition existed; the clinical picture, however, showing greater variety than the first case had led him to expect.

All cases had the following features in common:

1. Roentgenologically, cortical thickenings in the skeleton. So far, abnormalities were found in the skull, mandible, clavicles, scapulas, ribs, and the tubular bones of the extremities.

2. Tender swelling deep in the soft tissues. The distribution of the soft tissue swellings was roughly the same as that of the cortical hyperostoses, but small hyperostoses were visualized roentgenographically in several sites where soft tissue swellings had not been recognized clinically.

3. The abnormality disappears completely, leaving no traces whatever.

The majority of cases occur in early infancy, i.e. during the first three months of life, but a few cases were observed in children up to two years old. Subjectively, some of the children have pains and are irritable and troublesome. SMYTH (4), who was second in observing the same condition in 8 children, reports that they all had the same peculiar facial expression, caused by the swelling in the soft parts of the mandible. CAFFEY also described this peculiarity in cases where the disease sets in during the first 6 months of life. Other abnormal features found by both these authors were, fever; anaemia; leukocytosis; increase in the sedi-

mentation rate of the erythrocytes, or slight respiratory infections. Where there existed periosteal deviations along the ribs, sterile pleurisy was also present. No etiological moment was found, whilst all known causes of periosteal reaction could safely be excluded.

We ourselves had three of these patients under observation, which enabled us to note two features not present in the cases described by either CAFFEY or SMYTH, i.e.,

1. Occurrence of the abnormality in the patient's family.
2. Forward convex curvature of the thickened tibiae.

Case Reports.

Case I. A. v. H., girl, normal birth at term, Aug. 16, 1940 from healthy parents. When six weeks old, the child is brought to us by the mother, because for the last few days the left lower leg has been swollen. There is no pain in the leg, and the child shows no signs of being ill. She is breast-fed and is growing quite well. Weight: 3 880 g; Temp: 36.7° C. The child looks healthy and a general examination reveals no abnormalities. The whole of the left lower leg is swollen; the skin is not discoloured nor feels warm to the touch. The leg is not painful; motoricity is normal. No hypertrophy of the lymphatic glands. Wassermann and Sachs-Georgy reactions negative in both mother and child.

The roentgenogram (fig. 1) of Oct. 2, '40 shows a periosteal swelling on the medial side of the left tibia. The right leg is normal also radioscopically. No roentgenogram was taken of any other skeletal parts.

A week later, Oct. 9, '40 the swelling has increased; periosteal reaction now around the entire tibia and a roentgenogram taken lateral (fig. 2) shows marked forward curvature of the left tibia. On a radiogram of the thorax taken on Nov. 3, 1940, no abnormalities in the ribs are visible, but the clavicles are swollen. A double contour of the right humerus is seen.

On a radiogram taken five weeks after the first (Nov. 6, 1940, fig. 3) the swelling is seen to have further increased. Clinical observation (Nov. 7—20, 1940) reveals no other abnormalities; the temperature remains normal, except on the two days following the exploratory excision.

Exploratory excision from the tibia (Prof. Nieuwenhuyse): In the hard pieces of bone there is enormous infiltration of cell cords, with many osteoblasts around the edge. In the softer part about the same picture is seen, with infiltration on one side, of dark coloured nuclei containing little protoplasm, so that they appear to be lymphocytes. Amongst these lymphocytes marrow cells are also found.



Fig. 1. Case I. Roentgenogram on 10/2/1940, about one week after the onset of the disease. Periosteal swelling medial of the left tibia.



Fig. 2. Case I. Roentgenogram on 10/9/1940 of the left tibia in lateral direction. Periosteal reaction around the entire tibia.

Fig. 3. Case I. Roentgenograms on 11/6/1940 of the left tibia in anteroposterior direction (a), and in lateral direction (b), 6 weeks after the onset of the disease. The periosteal swelling has further increased.



Fig. 4. Case I. Roentgenogram on 11/19/1940, more than twelve months after the onset of the disease. The periosteal swelling has completely disappeared; the tibia is still curved forward.



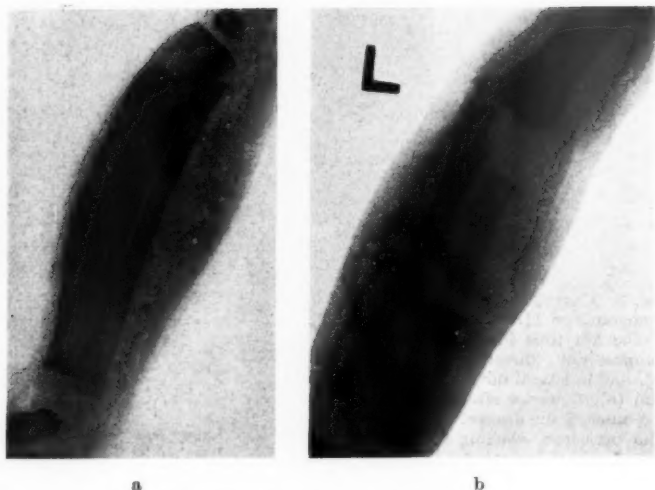


Fig. 5. Case II. Roentgenogram on 5/29/1946, about 3 weeks after the onset of the disease. Extreme periosteal reaction along right tibia (5 a), left radius, ulna and humerus (5 b). The tibiae are curved forward.

A culture test was made with the excised tissue, as well as the guinea pig test; in both cases the result was negative.

The leg was then irradiated a few times with roentgen rays. On April 25, 1941, a roentgenogram was taken, showing the thickening of the periosteum to have considerably decreased. By Nov. 19, 1941 it had disappeared completely. A radiogram shows the contours of the bone to be normal; the forward curvature of the tibia, however, is still present (fig. 4). Patient's general condition is excellent, and she has no difficulty in walking. May 19, 1947. No complaint whatever. Radiogram is normal, the tibia is straight.

Case II. H. v. H. (brother of the patient described as Case I); boy, normal birth at term, March 12, 1946. The father contracted syphilis about June 1944, for which he was treated in October 1944 (typical Lues II). The mother was treated at the same time for lues II also.

The boy is brought to us by his mother on May 23, 1946, being 2 months old, the mother has noticed for a few weeks that both his legs are swollen and painful. Apart from this the child is in excellent condition, thriving quite well on breast feeding.

Patient is a healthy looking child. A general examination reveals no abnormalities; no symptoms of congenital syphilis (clear skin, no

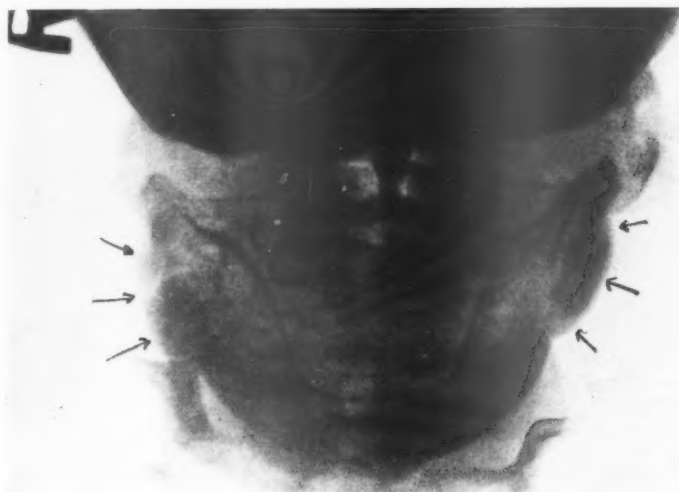


Fig. 6. Case II. Roentgenogram on 6/12/1946. Periosteal reaction along the rising processes of the mandible.

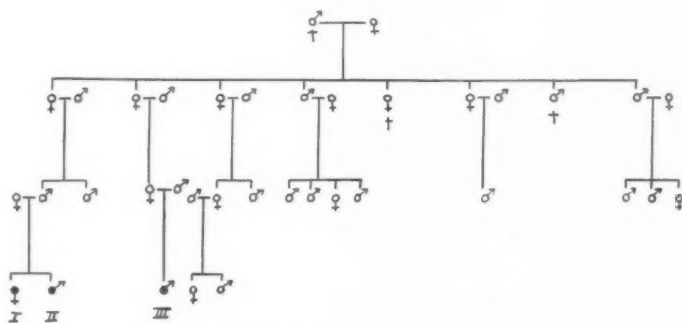


Fig. 7. Family tree, I, II and III are the patients. All other members of the family are in good health.

rhagades, no running nose, no enlarged spleen or liver). Wassermann and Sachs Georgy reactions negative in both mother and child.

Along the rising processes of the mandible a firm swelling is felt. The legs are tender to the touch. The distal ends of the upper and the lower legs are swollen; the lower legs curve forward. The skin is not dis-



Fig. 8. Case III. Photograph of patient on 1/10/1947, about 3 months after the onset of the disease. Swelling and curvature of the right lower leg are still clearly visible. The left leg shows the same deviations.

coloured and does not feel hot to the touch. Blood: Ca. 10.4 mg%, Phosphorus 4.6 mg%, Phosphatase 20 U (according to Jenner and Kay, normal: 8—17 U).

A roentgenogram taken on May 29, 1946 (fig. 5) shows periosteal reaction along the right and left tibiae, R. and L. humerus, R. and L. radius, as well as along the rising processes of the mandible (fig. 6). No radiograms were taken of other skeletal parts.

Admitted to the Wilhelmina Clinic on June 11, 1946. Wassermann reaction again negative in both mother and child, also after injection of 12.5 mg salvarsan. Blood: Hb. 55 %, Erythrocytes 3 580 000, leucocytes 12 000, eosinophylic leukocytes 2, unripe leuk. 10, segm. 34, lymphocytes 54. Sedimentation 20 mm.

The patient contracts a nutritional disturbance due to parenteral infection (mastoiditis) and dies 3 weeks after admittance to the clinic. Exploratory excision and autopsy refused by parents.

Case III. A. v. M., boy, normal birth, at term, July 9, 1946. Patient is a second cousin of the two preceding patients (vide family tree, fig. 7). His parents are healthy. The boy is brought to us on Oct. 24, 1946,

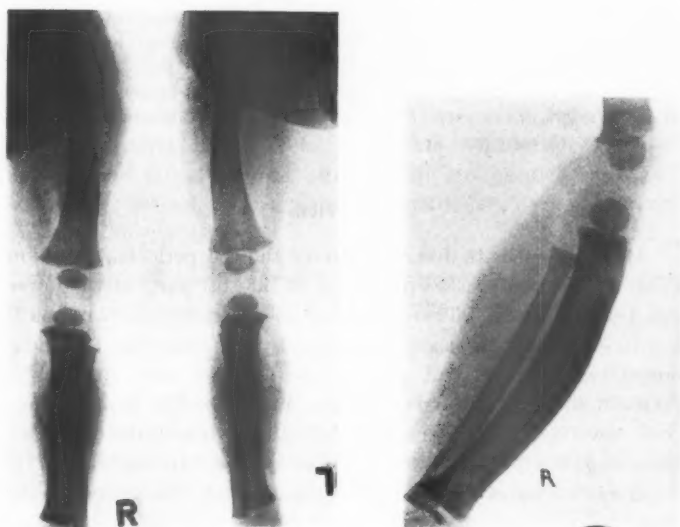


Fig. 9. Case III. Roentgenogram on 1/10/1947, 3 months after the onset of the disease. The periosteal thickening along the tubular bones is beginning to assume an osseous structure. Here too the tibia is curved forward.

when 3 $\frac{1}{2}$ months old, because the mother has noticed since a few weeks previously that his legs are painful and swollen, mobility being also impaired. Apart from this the boy is in good health and thrives properly on combined breast- and bottle-feeding.

Patient is a sturdy child with no abnormalities apart from the lower legs being considerably thickened and tender to the touch. The skin is neither discoloured nor warm to the touch. Lymph glands not swollen. No facial peculiarities. Wassermann and Sachs Georgy reactions negative in both mother and child.

The roentgenogram taken on Nov. 6, 1946 shows extreme periosteal swelling along the right and left tibiae, the femur, the radius, the ulna and the humerus. No roentgenograms were made of other bones. Clinical observation, exploratory excision and a thorough blood test were refused by the mother.

Dec. 10, 1946. No complaint whatever; the lower legs are still plainly too thick as well as curved, but no longer painful and mobility is good.

Jan. 10, 1947. Patient is in excellent condition and is growing well. Lower legs still swollen and curved (see foto, fig. 8). Blood picture: Hb. 84 %, Erythrocytes 6 820 000, leuk. 29 300, diff.: eos. 6, unripe leuk. 7,

lymph. 65, monocytes 5. Roentgenograms are now made of the entire skeleton, no abnormalities being found anywhere except in the parts already mentioned as being affected. The thickened periosteum of the long tubular bones is beginning to assume an osseous structure. On the lateral radiograph the patient's tibiae are also seen to be curved forward (fig. 9). No therapy was applied.

Discussion.

All three patients described above showed periosteal reaction along several bones, a deep swelling of the soft parts of the lower legs being palpable. There were no roentgenological abnormalities in either of the cases in the epiphyses. Only the last-mentioned two patients had pain in the legs for some time. One patient (case II) had slight anaemia; one (case III) leukocytosis. One (case II) died of intercurrent infection, while in the other two cases the disease had a favourable course. In one case (III) no therapy whatever was applied; in another, irradiation of the tibia.

No etiological moment was revealed in any of the cases. The father of the first two children contracted syphilis after the birth of the first child (in 1944), and was treated, as well as the mother, for lues II. Although, therefore, it is not entirely impossible that the second patient's abnormality is traceable to syphilis, this is improbable, since no stigmata were present, while the radiographs showed no epiphyseal abnormalities, and the Wassermann reaction were consistently negative, even after salvarsan injection. In any case this observation excludes the possibility of syphilis being the cause of the trouble in the first patient.

The typical facial expression described by SMYTH in similar cases observed by him was absent in our own cases. Nevertheless, in one of them the roentgenogram showed abnormal thickening of the mandible.

A typical feature in all three of our patients was the marked forward curvature of the tibiae.

Summary.

Three patients with infantile cortical hyperostoses (CAFFEY) are described. The only clinical symptom was swelling of the lower legs. Radioscopy showed extreme thickening of periosteum, also along parts of the skelet not swollen clinically. Features not hitherto described and observed in our patients were, (1) occurrence within the same family, and (2) marked forward curvature of the tibiae.

Read in summary before the »Nederlandsche Vereeniging voor Kindergeneeskunde», March 2, 1947.

Résumé.

On décrit trois enfants atteints de hyperostoses corticale (Caffey). Le seul symptôme clinique était un gonflement de la partie inférieure des jambes. Une radioscopie montre un fort épaissement du périoste, même au long de parties du squelette non-gonflé. Des faits non décrits ni observés jusqu'à présent chez nos malades étaient 1. des cas dans la même famille et 2. une courbure en avant des tibiae prononcée.

Zusammenfassung.

Bei 3 Patienten mit Rindenhyperostose im Kindesalter (Coffey) fand sich als einziges klinisches Symptom eine Anschwellung der Unterschenkel. Im Röntgenbild starke Verdickung des Periostes auch längs der klinisch nicht geschwollenen Skeletteile. Bei unsern Patienten bisher weder beschrieben noch beobachtet wurden: 1: das Vorkommen in derselben Familie, 2: eine ausgesprochene Verkrümmung der Schienbeine nach vorn.

Resumen.

Este artículo trata de tres pacientes con hiperostosis cortical infantil (CAFFEY). El único síntoma clínico que se observó fué tumefacción en las piernas. La radioscopia mostró un engrosamiento extremo del periostio, y también a lo largo de ciertas partes del esqueleto no clínicamente entumecidas. Las carac-

terísticas, hasta ahora no descritas ni observadas, de nuestros enfermos fueron: (1) casos en la misma familia y (2) marcada curvatura delantera de la tibia.

Leído en resumen ante «Nederlandsche Vereeniging voor Kindergeneeskunde», marzo 2, 1947.

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(FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT
NORRTULL'S HOSPITAL, STOCKHOLM. HEAD:
PROFESSOR A. WALLGREN.)

Primary Hemolytic Anemia in Infants.

By

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Stockholm. Stockholm.

The reason why we consider it proper to publish the following communication is that the three cases of primary hemolytic anemia in a few months old infants, who have recently been treated in the Norrtull's Hospital, represent certain extremes in the group of disorders with its varied flora of symptoms. Besides they illustrate conspicuously some less well-known aspects of the clinical features of the disease, which in infants also differ in certain important respects from the forms known in older children and adults. One of the cases is unquestionably hereditary and persisting, with a richly ramified pedigree of the disorder, the others possibly acquired, without any signs of heredity, and hitherto of an episodic nature. One case set on with jaundice and *acholic* stools, the second case with pallor and anemia, the third case with jaundice and anemia. The first case fulfills the requirements we make to establish the diagnoses, the latter cases suggests that the atypical form may possibly represent a distinct disorder.

The primary hemolytic anemia has had many different names, according to its changing symptomatology, only in a number of the cases will the term hemolytic icterus be adequate. Owing to the different clinical pictures the disease has been divided into several units. GÄNSSLEN and many subsequent authors have contested the justification of doing so and consider that we have to do with changing forms of manifestation of the same fundamental disorder and that all primary hemolytic disease is

of common genesis: The inherited constitutional anomaly, be it reflected in the morphology of the blood corpuscles or not. Right from the beginning two types have, however, been established which can justly be used, at any rate for descriptive purposes: The hereditary type contra the acquired type, also termed MIN-KOWSKY-CHAUFFARD's type respectively *typus* HAYEM-WIDAL after the authors who first described them, in which according to A. KIRKEGAARD & G. KIRKEGAARD the following dissimilarities can be demonstrated:

- 1) The acquired cases (Ac.) are of sporadic occurrence, without demonstrable heredity — that is how they are defined — in contrast with the «classical» hereditary forms (H.) of family-linked occurrence.

- 2) In Ac. severer anemia and more intense regeneration are found than in H. Besides the whole course is severer and evenly progressive, whereas in H. it is milder, oscillating about a state of equilibrium.

- 3) Spherocytosis may occur in both forms, but it is characteristic of H. that, with normal cell volume and index, decreased mean diameter and decreased osmoresistance are found. In the Ac.-forms an increased cell volume is associated with index less than 1, and normal or increased diameter of the erythrocytes, and rather frequently the resistance of hypotonic saline solutions is normal but not the resistance to heat or mechanical influence.

- 4) In Ac. surgical treatment with splenectomy results in total recovery, whereas in H. recovery is often incomplete, at any rate the spherocytosis and the decreased osmoresistance are generally found also after the operation.

There is hardly any doubt about the occurrence of sporadic cases, but in the individual case it may now and again be very difficult to ascertain that heredity is out of the question. GÄNSSLEN et alii have pointed out how great a number of the cases there may pass unnoticed if a thorough hematologic examination of the whole family is not carried through. It has, therefore, been desired to find a criterion of classification that can be demonstrated in the patient himself. THOMPSON suggested to use the spherocytosis as a basis, just as the sickle cell and the large thin erythrocyte are pathognomonic each of its erythrocyte

anomaly: The «sickle cell» anemia in negroes, Cooley's erythroblastic anemia in the Mediterranean peoples. This classification of hemolytic anemia into spherocytic and atypical h. a. does not coincide with that of hereditary and acquired forms, and it is difficult to see the advantages that may be associated with it.

No classification has proved to be satisfactory for the purpose of grouping all cases. Among others SUTTON & MOORE have demonstrated this fact in connection with the reporting of some cases in which the symptoms changed so much in the course of the disease that now they had to be included in one, now in another clinical type.

Viewed as a whole it will be seen that there exists a number of facies morbi which, with an even transition, range from the «classical» complete symptom complex via the more or less compensated forms («stunted varieties») to monosymptomatic, often mis-judged forms and fully compensated forms of hemolytic anemia in which, only accidentally or out of suspicion owing to relationship with a patient, a so complete examination of the blood is carried out that will cause the signs of hemolysis on a constitutional basis to be discovered.

The obligatory symptoms are few:

1) Bilirubinemia can always be demonstrated, but in moderate hemolysis it is frequently so slight that (according to COOLEY) the icterus index or the van den Bergh's test are not of much value, so long as the liver excretion is free.

2) Increased excretion of bile pigment, which ought to be the exact exponent of the hemolysis if we both had a clinically useful method for quantitative determination in the feces and were able to eliminate the error originating from the reabsorption of bilirubin derivatives from the intestines.

3) Splenomegaly is always found and while it always becomes palpable in children, GÄNSSLEN states negative palpation result in 30 per cent. of his «adult» patients. Both DEBRÉ, J. ABT and A. F. ABT find it as a constant symptom in children.

4) Hyperplastic, normoblastic reaction of the bone marrow with appearance of nuclear erythrocytes in the blood stream and considerable reticulocytosis and anisocytosis.

The remaining symptoms are all of them more or less inconstant, this even applies to so characteristic phenomena as spherocytosis, microcytosis and decreased osmotic resistance, which were once considered necessary to establish the diagnosis. The two symptoms that in the complete, the «classical» facies morbi take up so prominent a position that they have lent the name to the disease, anemia and jaundice, are strangely enough, not obligatory.

Most frequently the anemia is marked, and always so in crises, but may be absent as a clinical symptom in cases where the regeneration manages to keep pace with the destruction. Such stunted varieties are believed by GÄNSSLEN to be seen in 35 per cent. of the cases, far more rarely during childhood and most rarely in infants, in whom the hematopoietic apparatus has the least reserve power.

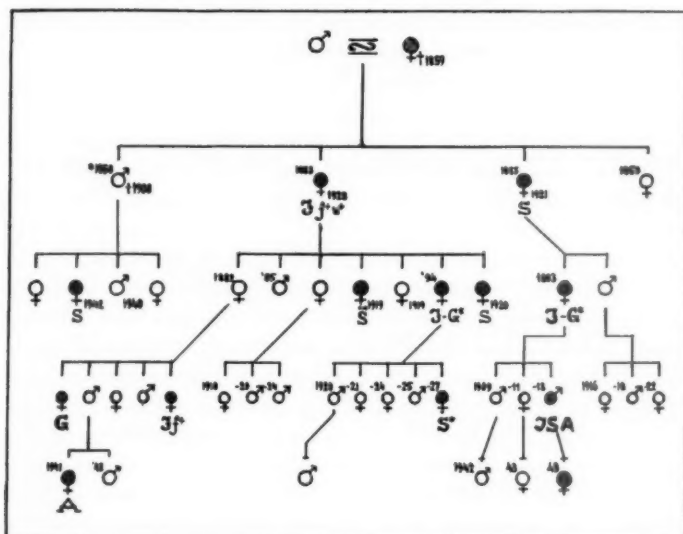
Although jaundice is a main symptom it is inconstant — the more, the younger the individual is. It may remain latent for years or decades and is suppressed as long as the liver function is normal. Therefore, it is almost always lacking in children under school-age (DEBRÉ). HOLT states that before a hemolytic anemia in children may cause visible jaundice the excretory capacity of the liver must be reduced so much that a certain hepatic insufficiency can be said to be present. Each of the two symptoms thus depend on the functional capacity of its separate organ, for which reason they vary in intensity rather independently of one another.

Defectiveness of the blood corpuscles, whether the defect manifests itself morphologically as microcytosis—spherocytosis or can be demonstrated as a decreased osmoresistance, is not a pathognomonic finding as was first believed — on the contrary, it is lacking in a great percentage of cases. It is stated that decreased osmotic resistance is not demonstrated in 10 per cent. of the cases in adults (GÄNSSLEN) and without reference to the percentage it is stated that this symptom (as well as microspherocytosis) is often lacking. It has been possible to demonstrate hemolysins (lienogenic?) only in a small percentage of cases.

The clinical picture of the disease in children is not fundamen-

tally different from that seen in adults; there is no type of the course that is specific of childhood but the tendency is that the younger the child, the greater is the preponderance of the incomplete syndromes, the compensated forms of the course. After observation of his 14 families of hemolytics DEBRÉ concludes that jaundice-anemia and decreased resistance in childhood are very inconstant symptoms, «stunted varieties» of the disease being the rule, at any rate before the 7th year. Fever is frequently seen, it may be continuous or occur periodically with slight jaundice by attacks as hyperpyrexia with intense jaundice, or with fatal attacks of anemia. Enlargement of the spleen is always found, with exacerbations at the crises, possibly so seriously that the predominant feature is abdominal symptoms with pain and vomiting.

When the disease occurs in infants its manifestations become less typical. In families known to comprise hemolytics it has sometimes been possible to ascertain an aniso-microcytosis and decrease of resistance of the red blood corpuscles already in the newborn infant before any clinical symptoms whatever had appeared. HAWSKLEY describes a 2-days-old child of a family in which 2 out of 4 elder sisters and brothers suffered from hemolytic jaundice and in whom a marked hemolysis occurred with saline solutions of 0.45 per cent. as compared to the solutions of 0.39 per cent. that are normal at that age. The size of the blood corpuscles was 7.12 as compared to the normal 7.99. After a little over one month the patient became anemic, icteric and the spleen became palpable. The facies morbi was thus fully developed then. BECK described the case of a 5-months-old infant who had been yellowish pale even from the birth but was only examined at the age of 5 months when the anemia was ascertained. — Most cases of congenital hemolytic jaundice are only revealed at more advanced ages, many of them doubtless being so well-compensated that they are not revealed at all without special and thorough examination. On the basis of their own 3 cases and a comparison with the rather few cases previously reported in the literature A. F. ABT and J. ABT state that the blood findings prove to be very inconstant, even if the hyperchromatic anemia and the re-



J: jaundice A: anemina
 S: subacute splenomegaly G: gallstones
 J: adult jaundice W: Wilson's disease * sporadic case

Fig. 1. Pedigree-tree from case 1.

generative processes were very marked. The jaundice is most frequently faint. The diameter of the erythrocytes and the resistance may be decreased, normal, or increased, with or without spherocytosis. Fever and distinct leukocytosis were found only in 1 out of 3 cases.

Case 1. A female infant, aged 2 months, was admitted to the hospital because her mother had observed a distinct change of colour of her stools. As the girl was breast-fed they had previously had the golden yellow colour characteristic of the stools of breast-fed infants but had now suddenly assumed a milkwhite tinge. On the same day she had also a yellow discolouration of her face. She was previously in good health, possibly somewhat pale. Her mother did not know of any infectious disease in their surroundings, but she was able to tell a good deal about the family into which she had married. After subsequent additional information her statements can be reproduced in the following pedigree (fig. 1).

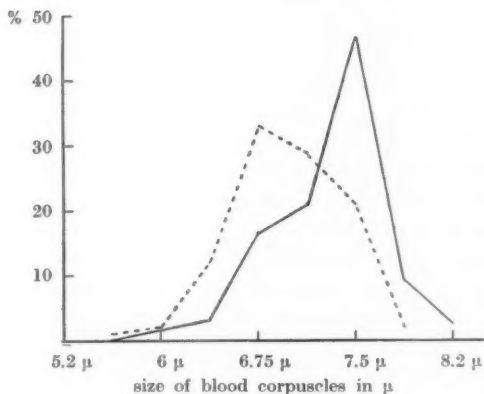


Fig. 2.

Erythrocyto-gram.

----- = pat. (200 blood corpuscles measured).
 ————— = patients at corresponding age.

With this massive heredity of hemolytic jaundice we of course, suspected that the girl suffered from the same disorder. With the following results of the laboratory examinations we were able to establish the diagnosis: 1) Incipient hemolysis with hypotonic saline solutions at 0.55 (as compared to the normal 0.44) total hemolysis 0.40 (as compared to the normal 0.34). 2) Meulengracht's test 1:18. Hijman van den Bergh's test indirect positive, direct faintly positive. 3) Anemia of 56 per cent. hb, about 3 mill. red blood corpuscles. 4) Between 5 and 16 per mille reticulocytes, and 5) Price-Jones curve of size of the blood corpuscles and dispersion as will appear from the erythrocyto-gram (fig. 2). It displays a tendency that is absolutely typical of primary hemolytic jaundice, tending towards microcytosis.

Of other examinations, which were only of a more indirect importance to the diagnosis, the following will just be mentioned:

Wassermann's test was negative both in mother and child; they were of the same Rh-group, both of them;

serum phosphatase and citric acid displayed no deviation from the normal values;

6) now and again the spleen was evenly palpable; urine and stools contained no bile pigment.

Comments: The symptoms causing the parents to consult a doctor, the occurrence of acholic stools, cannot be included among

those generally characterizing a case of hemolytic jaundice. On the contrary, an increased amount of bile pigment in the stools is stated to be characteristic of this disorder. Before trying to explain the possible connection, we shall briefly recapitulate what else is known about the occurrence of bile pigment in the stools and urine of breast-fed infants. For conditions are not the same in infants and older children, in bottle-fed and breast-fed infants.

Bilirubin (but not urobilin-stercobilin) is of normal occurrence in the stools of breast-fed infants. This is not the case in bottle-fed infants and older children, in whose stools only urobilin-stercobilin can chiefly be demonstrated. The bacterial flora that is capable of converting (oxidizing) bilirubin into urobilin is not present in breast-fed infants. As urobilin is only produced in the intestines, urobilinuria can, therefore, never occur in breast-fed infants either. Schlesinger's fluorescence test is not specific. In hemolytic jaundice a larger amount of bile pigment is present in the intestines. The whole of it is not converted into urobilin-stercobilin in the course of the passage through the intestines (this is what applies to older individuals) but bilirubin can even be demonstrated in the former. The same holds good in the case of rapid passage through the intestines. In breast-fed infants there is only the difference that the amount of bilirubin increases — the serum bilirubin can only be excreted with the urine when it has reached a certain concentration. This threshold value is considerably higher (about 20 mg%) in the new-born than in adults (3 to 9 mg%), which is probably due to a physiologic insufficiency of the kidney of the new-born (LARSEN & WIT 1943).

In the present case it would thus have been expected that bilirubin could have been demonstrated in the stools and possibly even in the urine. No bile pigment was, however, found here. That the supply of bile acids was also shut off appeared from the quantitative analysis of the stools, which showed a considerable increase (about twice the normal value) of the total fat which comprised 90 per cent. free fatty acids and soaps, thus certainly decomposed but not resorbed.

The explanation we would offer of the symptom acholic stools in this case is the following: The fundamental disorder is hemolytic

jaundice. In a hemolytic crisis the increased destruction of the blood leads to a thickening of the bile, formation of bile thrombi and increased calculus formation. The pedigree, too, will doubtless also suggest that there is a connection between hemolytic jaundice and gall stones, as at least 3 of the members of that family have been operated for cholelithiasis. PEMBERTON found that 25 out of 118 of his cases that had been splenectomized for hemolytic jaundice had been previously operated on for gall stones without the true diagnosis being established. In $\frac{2}{3}$ of the cases treated by MAYO with splenectomy he found stones in the gall bladder or the gall ducts. In 3 out of 10 splenectomized children stones were found in the gall bladder, having not been suspected in any of the cases before the operation (BARRINGTON-WARD).

A roentgen examination might be expected to reveal possible concrement. Neither with nor without contrast medium did any calculi appear, the gall bladder could not even be filled. Unfortunately, the examination was only carried out after the course of a few weeks. The stools had already then begun to assume the normal colour. It is doubtful how such findings (failure of filling with contrast medium) should be considered. In order to arrive at an idea of the possibilities of demonstrating the gall bladder by means of roentgenoscopy after administration of contrast medium we had a number of healthy infants of different ages X-rayed but had to interrupt the examinations after 2 of the children came into a state of acute shock. The medium used is the one that has been employed in this ward during the past few years, iodotetragnost (tetraiodophenolphthalein sodium). The splitting off of iodine in the organism is considered slight and without any risk, but as an additional precaution a preliminary test was even made with potassium iodide. The dose of contrast medium is very large as compared to the one used for adults ($\frac{1}{2} \div 1$ g respectively $4 \div 4$ g). In the 5 infants under the age of 7 months in whom the examination was uncomplicated the gall bladders were not filled. We do not venture to draw any conclusion from this fact but believe we are justified in questioning the value of that method of examination in the case

of so small children. In children who are a little older (> 7 months) the filling succeeded as usual.

In conclusion a few words will be said about the course up to now. After the course of 1 or 2 weeks the stools gradually assumed a yellowish green colour and have been normal ever since. The anemia keeps within modest limits (about 60 per cent.). Reticulocytes: 10 per mille. No bilirubinemia, no enlargement of the spleen. The general development somewhat retarded. The girl is now 18 months and up to now she has displayed no anomalies of the bones which can be attributed to the increased activity of the bone marrow and are said to be a complication that can be expected in patients with hemolytic jaundice during infancy.

Case 2. Male infant. After completely normal delivery and a neonatal period without any jaundice the child developed satisfactorily in every respect, he was breast-fed with an addition of citric-acid-milk from the 7th week. Already at birth the child was strikingly pale and remained so despite liberal exposure to sunlight. The stools were darker than normally in infants but never like melena. The colour of the urine was always normal. There were no symptoms of hemorrhagic diathesis and no loss of blood of other causation, as for instance external hemorrhage.

The pallor as a sole symptom was acutely aggravated in the 9th week, but the general health was still uninfluenced and there was no fever or dyspepsia when, on Aug. 25th, the patient was admitted to Norrtull's Children's Hospital.

On admission the following symptoms were found:

Marked, yellowish white pallor with hemoglobin percentage = 39 and 2.45 mill. erythrocytes per emm (index = 0.85) with 1.9 per cent. reticulocytes and a high sedimentation rate 65 mm). Slightly increased consistence of the liver without safe signs of hepatosplenomegaly.

On the 3rd day the anemia reached its maximum: 900 000 erythrocytes with a hemoglobin percentage of 23, for which reason a blood transfusion was made.

The state of the blood during the period that followed will appear from the curves in Fig. 3. During the first 2 weeks there was slight bilirubinemia (Meulengracht 1:11 and 1:10), later on the index was below 1:8. There was no leukocytosis but, at times, relative lymphocytosis. Times of bleeding and coagulation were normal, the thrombocyte figure was fairly high, never below the lower limit of the normal. On the 5th to 10th days the prothrombin index was about 50 per cent., for which reason vitamin K was administered during the next 4 weeks.

%
90
80
70
60
50
40
30
20
10
0
Hemoglobin
Reticulocytes
Spleen
WBC
Thrombocytes
Leucocytes
Lymphocytes
Prothrombin
Sedimentation

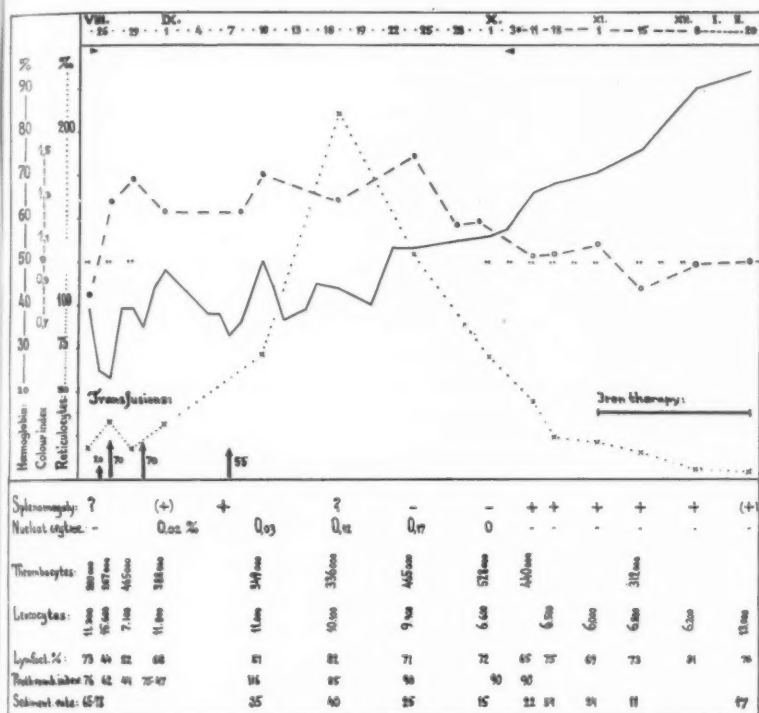


Fig. 3.

On repeated determinations of the erythrocyte diameter the Price-Jones curve differed only a little from the normal, displayed no microcytosis but a slight macrocytosis. No spherocytosis could be demonstrated. On several successive examinations the resistance was normal, the hemolysis beginning at 0.40 to 0.42 per cent., being complete at 0.32 to 0.36 per cent.

Determination of the blood groups gave no clue to Rh-immunization between mother and child, their bloods being of the groups O—M—N—Rh + and A—M—Rh + respectively. No irregular agglutinins were demonstrated. Wassermann's and Kahn's tests were negative in both of them.

There was nothing in the family anamnesis that could be interpreted as occurrence of hemolytic disease or its sequelae. Examination of the

family only comprised the parents; the state of the blood was completely normal in both of them, there was no reticulocytosis or bilirubinemia.

Therapy and course:

On Aug. 26th blood injection (20 cc intramuscularly) and from Aug. 27th to Sept. 7th 3 transfusions: Twice 70 cc intravenously, then 55 cc intraperitoneally. After the transfusion on Aug. 27th the hemoglobin percentage rose temporarily, the procedure had to be repeated on the 6th and 14th days, but the persisting effect on the hemoglobin percentage became rather slight, considering the amount of blood administered. Just before the last transfusion the inferior pole of the spleen became distinctly palpable.

Sternal puncture on Sept. 3rd revealed a severely injured bone marrow, suspect of a systematic disorder of the reticulosis type. The erythropoiesis was slightly hyperplastic and there was grave interference with the process of maturation. The reticulum was highly hyperplastic with partially marked proliferation of monocytoïd cells.

At this time there were still no signs of a more vigorous regeneration in the circulating blood, but in the 3rd week the reticulocytosis quickened and displayed all accompanying symptoms, such as anisocytosis etc. It reached its maximum in the 4th week, subsiding gradually in the course of the weeks that followed. At the same time the patient became livelier, his general health improved and his weight began to increase again, by 100 to 400 g a week, 1 900 g in the course of 9 weeks. On Sept. 22nd the iron content of the serum was 0.154 mg%.

The spontaneous improvement of the blood values has since continued regularly without any treatment whatever; from the 5th month of his life the patient however, got a daily dose of iron (the preparation »Guttafer») until, at the age of 8 months, he reached a hemoglobin percentage of 94 with normal colour index and 0.4 per cent. reticulocytes.¹

Neither bilirubin nor urobilin was ever demonstrated in the urine.

¹ In order to be sure that the recovery observed was not merely a transient one, this article was withheld from publication until a control investigation of the blood of this child had been made 12 months later (on Feb. 20, 1947). The child has now reached the age of 18 months.

The somatic and mental development of the infant has run a fully normal course; he began walking and chattering a number of words at the age of one year. Now, at 1 $\frac{1}{2}$ years age, he is capable of saying sentences of 5 to 8 consecutive words, and to a certain extent of helping himself at meals. He has had no infections during the past 12 months, and has shown no pallor.

The weight is now 11 340 g. Physical examination revealed normal conditions, the antero-median fontanelle being closed, and the lymphoid tissues not enlarged; the spleen was palpable one inch beneath the lower ribs, however. *Blood examination:* hemoglobin 81 per cent with normal colour index, reticular cells 0.1 per cent. Size and shape of erythrocytes within normal limits.

When a grave anemia occurs in infants (or older children) and — as in the present case — neither erroneous nutrition nor an external loss of blood can be made responsible of the disorder, there will be reason to suppose that the anemia reflects a hemolytic process, provided the erythropoiesis proves to be intact. This suspicion is especially well-founded in case of abrupt falls of the hemoglobin percentage but also called for when an inexplicable anemia of a fairly constant degree occurs at a young age.

In this case a pallor, a constantly yellowish pale complexion, observed right from the first time of life was mentioned in the anamnesis, as in the case reported by BECK. The colour of the stools was often darker than the normal. The patient's general health was otherwise satisfactory until the onset of the crisis; and the development took a normal course. Without any demonstrable releasing cause whatever, without any other preceding or simultaneous disease a severe hemolytic crisis occurred during which, in the course of 3 days, the hemoglobin percentage fell to 23. Slight general prodromes ushered in the crisis, but the patient was afebrile and his general health strikingly uninfluenced.

Proof of the hemolytic nature of the case had been established, as 1) bilirubinemia was demonstrated, i.e. increased formation and excretion of bile pigment, reflecting an abnormal destruction of erythrocytes; 2) enlargement of the spleen was found, and 3) a reaction on the part of the bone marrow, increased erythropoiesis, marked by vigorous reticulocytosis and the occurrence of erythroblasts in the blood-stream, were demonstrated.

It applies first and foremost within the scope of the primary hemolytic anemia that the remaining symptomatology is so changing from one case to another that the diagnosis is not precluded, although more or even most of the features characteristic of the fully developed facies morbi might be lacking.

Besides primary constitutional hemolytic anemias a number of hemolytic conditions of secondary nature occur in childhood as well as in adult patients; and while the former constitute a fairly well-defined entity the latter group comprises a number

of highly different conditions, the heterogeneous etiology of which renders a perspicuous classification difficult.

Under the same clinical picture as the primary hemolytic anemia a symptomatic h. a. may develop as a sequela in a number of malignant disorder — as it *seems* on a non-constitutional basis — and may occur as a complication in leukemia, lymphogranulomatosis, carcinomatosis and a few other diseases (DAVIS).

A moderate or slight hemolysis may also be present as a secondary phenomenon in certain chronic infectious diseases as lues or malaria, or in acute disorders, thus often in children with acute infections on the whole; and moreover in predisposed individuals quite trivial infections may release so intense a hemolysis that it becomes the predominant symptom, episodic as in the so-called LEDERER's anemia, or subchronic as in VON JAKSCH-HAYEM's syndrome.

Moreover a great number of substances is known which, when introduced into the organism even in small amounts, will produce lysis. Besides organic hemolysins as isoagglutinins (including that of the Rh-factor), bacterial hemolysins, snake venoms and others, there are organic and inorganic hemolytic toxins, e.g. lead, arsenic acid, phenylarsine, and other arsenic compounds, phenothiazine, saponal substances. In cases where sulfonamides, certain seeds (horsebean, in favism) and species of pollen (the vernal anemia in Bagdad) release hemolytic anemia the genesis has been demonstrated to be a hypersensitiveness, an allergy (DAVIS).

It would have been possible to find a reasonable explanation of the afebrile crisis if any substance of the above group could have been demonstrated as the cause of the disorder, but this was not the case. A special interest was taken in the Rhesus factor, but a serologic examination could exclude this genesis of the anemia; already the occurrence of the crisis so late as several months after a normal neonatal period went against this etiology.

There were no signs of other diseases, neither acute infections nor chronic disorders: No catarrhalia or sepsis, no clinical or serologic signs of lues in the child or the mother, or malaria still less in the afebrile course.

On the whole a crisis most frequently takes a febrile course. And in that case it is possible now and again to misjudge a few other conditions, even though it will as a rule be an acute manifestation of the congenital hemolytic anemia. A leukemia will set on acutely with a hyperpyretic crisis, severe anemia and intoxicated general condition. The relapsing course, the glandular swelling in connection with the abnormal leukocyte picture will soon establish the diagnosis. In this case there was nothing that could be interpreted in that direction, and the absence of fever and leukocytosis as well as vomiting and diarrhoeas made it unwarranted to consider the disease a Lederer's anemia, with which the condition still had something in common, namely its episodic character: The acute onset with chiefly spontaneous regression in the course of a few weeks, leading to complete clinical recovery.

The peculiar findings in the sternal puncture suggested the possibility of a reticulosis, but the regeneration that occurred so soon and the subsequent course rendered the diagnosis improbable. — It is most reasonable to reckon with the diagnosis of primary hemolytic anemia.

There are several facts in our case that are peculiar and render it difficult to place the case:

1. Heredity has not been rendered probable through anamnesis or hematologic examination of the parents, even though the anamnesis distinctly points in the direction of a congenital condition.

2. It has been impossible to find out any releasing cause that would justify the term secondary hemolytic anemia, but the long »latent period» speaks in favour of a passing insult as the cause of the crisis: 2 or 3 weeks passing between crisis and erythropoietic reaction as reflected by the sternal puncture. A hyperplasia of the lymphatic glands occurred simultaneously with the climax of the regeneration processes.

3. The regeneration continued till complete clinical recovery had occurred with normal hemoglobin percentage, normal reticulocyte per mille and plasma colour figure, and the recovery seems to persist.

4. The anamnesis, the afebrile course without leukocytosis, crisis without gastrointestinal or general symptoms go against an acute case of Lederer's type.

Case 3. Male infant. In this case the diagnosis was made when the child was 7 $\frac{1}{2}$ months old. During previous periods in hospital the real nature of the disease had not been detected. The weight at birth was 3 990 g. On the third day of life the patient had been noticeably icteric, the yellow discoloration of the skin persisting for 2 weeks. The patient had always been very pale, but had gained in weight satisfactorily. He was a breastfed baby. At the age of 2 months the hemoglobin was 42 per cent., red blood cells 2.4 mill., whites 16 000, reticulocytes 6—7 per cent. Fragility of the blood: beginning hemolysis at a concentration of 0.60 per cent. NaCl, complete hemolysis at 0.40 per cent. NaCl. The spleen was palpated at a spot one to two fingers' breadth below the arch of the ribs. A blood transfusion was given. At 7 $\frac{1}{2}$ months the hemoglobin was 56 per cent., red blood cells 3.6 mill., whites 17 400, thrombocytes 400 000, reticulocytes 39 per cent. Fragility of the blood: beginning hemolysis at a concentration of 0.40 per cent. NaCl, complete hemolysis at 0.35 per cent.; bleeding time and coagulation time normal. Differential blood count showed normal values of the white blood cells. As regards the erythrocyte sedimentation test the layer at the border between plasma and blood corpuscles was cloudy and indistinct (nebulous sedimentation). The serum iron was 0.103 mg per hundred cc of blood. The spleen had a hard edge and was palpable one to two fingers' breadth below the arch. Wassermann reaction negative. Rhesus agglutination test positive. This test was also positive in the mother. Epicanthus and strabismus were present. Roentgenexamination revealed nothing unusual in the skeleton.

The mother had been anemic during her pregnancy. The hemoglobin, red, white, and differential blood counts, size of the erythrocytes, and fragility of the blood all appeared to be normal. The patient's grandmother had suffered from biliary colic and anemia but an examination of her blood yielded nothing of interest. There were no other relevant family particulars.

At a control examination when the child was 2 $\frac{1}{2}$ years of age it was noted that since the age of 1 year the situation had been gradually improving as regards the blood. The hemoglobin was 72 per cent., red blood cells 4.2 mill., whites 8 400, reticulocytes 11 per cent., Meulengracht 1:18, sedimentation rate 7 mm in 1 hr. Spleen palpable.

Comment. The signs and symptoms of anemia with reticulocytosis, splenomegaly, decreased osmotic resistance of the red blood corpuscles (temporary), and microcytosis indicates the

diagnosis hemolytic anemia. In this case also, there was nothing to prove that the disease was inherited. The spontaneously occurring improvement from the age of 1 year is a remarkable feature of the case.

Summary.

The first case described is that of a 2-months-old breastfed infant belonging to a family of hemolytics who is taken ill with jaundice and acholic stools. The explanation of the symptomatology is that the increased decomposition of the blood in a crisis gives a thicker bile with risk of bile thrombi and obstruction of the flow of bile.

The possibilities and the risks of examining the gall bladders by means of iodine contrast media in infants under 7 months are discussed.

The second case is one of presumably congenital, not demonstrably hereditary hemolytic anemia, developing a severe, afebrile hemolytic crisis in the 9th week of life. To all appearances independently of the therapeutic measures the patient recovers in the course of 3 1/2 months, and at control 12 months later the blood findings revealed no signs of disease.

The third case presents signs of hemolytic anemia shortly after birth, with spontaneous and almost complete regress at the age of one year.

Résumé.

Le premier cas décrit est celui d'un enfant à la mamelle de 2 mois appartenant à une famille hemolytique et qui est atteint d'un ictère et avec des selles alcholiques. L'explication de la symptomatologie est que la décomposition du sang pendant une crise donne une bile plus épaisse avec le risque de thrombose de bile et obstruction de l'écoulement de la bile.

Les possibilités et les risques d'un examen de la vésicule biliaire au moyen de «iodine contrast media» chez des enfants de moins de 7 mois sont discutés.

Dans le deuxième cas il s'agit d'anémie congénitale, non pas démonstrativement d'anémie hemolytique héréditaire, qui oc-

casione une crise sérieuse, afébrile et hemolytique dans la 9ème semaine de la vie. Le malade se rétablit dans les trois mois et demi indépendamment des mesures thérapeutiques en apparence, et lors d'un contrôle effectué 12 mois plus tard l'état du sang ne montre aucun signe de maladie.

Dans le troisième cas on trouve des signes d'anémie hemolytique peu de temps après la naissance avec une regression spontanée et presque complète à l'âge d'un an.

Zusammenfassung.

Ein Fall von Gelbsucht mit acholyschen Stühlen bei einem 2 Monate alten Brustkind aus einer hämolytischen Familie. Die erhöhte Blutzerersetzung während einer Krise verdickt die Galle und kann Gallen-Thrombose und behinderten Gallenabfluss veranlassen. Möglichkeiten und Gefahren einer Untersuchung mit Jodkontrastmittel bei jungen Säuglingen werden besprochen.

Eine vermutlich kongenitale, nicht erbliche hämolytische Anämie mit einer schweren afebrilen hämolytischen Krise in der 9. Lebenswoche kommt unabhängig von Therapie im Laufe von 3 1/2 Monaten zur Ausheilung.

Ein Fall mit Zeichen von hämolytischer Anämie kurz nach der Geburt heilt im Laufe des ersten Lebensjahres spontan fast vollständig aus.

Resumen.

El primer caso es el de un niño de 2 meses, amamantado y perteneciente a una familia hemolítica enferma de ictericia y de deposición acólica. La explicación de la sintomatología es que la descomposición aumentada de la sangre en una crisis produce una bilis más gruesa, con el peligro de trombos de la bilis y obstrucción del flujo de la misma.

Se discuten las posibilidades y peligros de examinar la bilis de la vejiga por medio de medios de contraste de yodo en niños de menos de 7 meses.

El segundo es un caso de anemia hemolítica, presuntivamente congénita, pero no demostrablemente hereditaria, que produjo una crisis hemolítica afebril y seria en la novena semana de vida.

El enfermo al parecer recobró la salud independientemente de las medidas terapéuticas a los tres meses y medio; al efectuarse 12 meses después un control los hallazgos de sangre no revelaron ninguna señal de enfermedad.

El tercero es un caso que demuestra señales de anemia hemolítica brevemente después del parto, con regresión espontánea y casi completa a la edad de un año.

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Chronic, Non-familial Hemolytic Anemia in Infants.

By

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It is generally accepted that familial hemolytic icterus may occur in children, even in infants. The diagnosis is based upon the usual signs and symptoms of a hemolytic anemia, including marked regenerative changes in the blood and in the bone marrow, and also microcytosis, spherocytosis, decreased red cell fragility to hypotonic saline solution, and a familial occurrence. The disease often runs a latent course during childhood, or it may manifest itself by a slight jaundice only, otherwise not producing any serious symptoms. It is said that these patients are more jaundiced than sick. However, cases in which the disease becomes manifest in early infancy, often appear to be of a malignant nature (MEULENGRACHT, LICHTENSTEIN).

Now and then one might come across cases of hemolytic anemia in infants and children, presenting a clinical and hematological picture in several respects differing from the classical familial hemolytic icterus. ABT has described three cases of serious hemolytic anemia, the symptoms in one infant noted at birth, in the two others at the age of 4—5 months. A common feature in all cases was a severe anemia, with a hemoglobin content as low as 30—36 per cent and a red cell count down to 800 000. Obviously the anemia was hemolytic in nature with a marked reticulocytosis (up to 35 per cent) and an increased icterus index. However, two of the cases presented moderate jaundice only. It was also remarkable that the red cell resistance to hypotonic saline solution was normal in two of the cases, and that microcytosis or spherocytosis could not be demonstrated in these two patients. On the contrary, a

macrocytosis was present. The spleen was enlarged in all cases. Two of them were cured by splenectomy. No familial occurrence could be traced in the three cases reported. ABT emphasizes that microcytosis and decreased erythrocytic resistance to saline solution — symptoms which must be ascertained in order to diagnose familial, hemolytic icterus in older children and adults — need not be present when infants are concerned.

In the Pediatric Clinic, we have had the opportunity to observe two children presenting a picture very similar to that described by ABT.

Case 1. Solveig H., born May 5th, 1944. An only child. The child was born 3 months prematurely. Birth weight 2 300 g, length 46.5 cm. Mixed nutrition. She was first admitted to the hospital when she was 3 months old. The mother informed us that the baby from birth had been extraordinarily pale. The skin was yellow the first week, but later on no yellow tinge could be observed. On admittance the infant was very pale with a yellowish tinge. The liver and the spleen were obviously enlarged. Craniotabes, but otherwise no signs indicating rickets. Blood findings: The hemoglobin content was 34 per cent, the red blood cells numbered 2 000 000 per cubic millimeter, the colour index was 0.90, the leukocytes numbered 11 900 and the thrombocytes 249 000. The reticulocytes were 40—238 per thousand. A stained blood smear revealed 36-79 nucleated red cells per 100 white. The erythrocyte diameter was 7.8 microns estimated by the Halo test. Serum iron was 187—204 γ per cent. A test of fragility to hypotonic saline solution showed partial hemolysis at 0.38 per cent, complete hemolysis at 0.28 per cent. Tibial puncture revealed a hyperplastic bone marrow, mainly consisting of nucleated red cells at different stages of development (approximately 75 per cent of the nucleated cells belong to the erythropoietic system). Urobilinuria was noted. The serologic test (BWR) was negative. Following two injections of Campholone a temporary increase of the reticulocytes was noted, but no corresponding increase in the hemoglobin content. Iron administration was — as might be expected when the serum iron is high — without effect. She was given blood transfusions, and thus the hemoglobin content rose to 72 per cent. Subsequently she has repeatedly received treatment in the Pediatric Clinic, six times hospitalized, but otherwise followed in the out-patient department. The hemoglobin content has varied between 39 and 85 per cent. As a rule, blood transfusions had to be given every 3—4 weeks. The above mentioned signs of hemolysis have constantly been present. The degree of hemolysis varied, but no definite crises were noted. The health condition in general suffered when the hemo-



Fig. 1. Caput natiforme in case 1 at the age of 1 year.
Note the protruding tubera frontalia.

globin content was running too low. A caput natiforme developed gradually (fig. 1).

Splenectomy was performed on February 8th, 1946. The operation was uneventful. Prior to the operation the hemoglobin content constantly went down to 40 per cent during a period of 3—4 weeks, sometimes in the course of few days. After the splenectomy the hemoglobin level remained constant at 80 per cent the first six weeks. Subsequently there was a gradual decrease reaching 60 per cent on April 25th, when she again received a blood transfusion. This has been repeated every 6—8 weeks, but the hemoglobin content did not fall below 60 per cent during this period. The reticulocytosis and the other signs of hemolysis remained unchanged after the operation. The removed spleen weighed 60 g. Microscopically there was a marked fibrosis, hyperplastic trabeculae, and a diffuse, hyperplastic sclerosis of the vessels. A Turnbull-stained section revealed abundant quantities of blue-colored pigment.

A girl has been pale from birth with a slightly yellowish tinge. First examination at the age of 3 months revealed a considerable hemolytic anemia (hemoglobin content 34 per cent). The condition did not respond to any kind of therapy except blood transfusions, which temporarily would cause increase of the hemo-

globin content. The transfusions had to be repeated every 3—4 weeks. At the age of 21 months splenectomy was performed.

The hemoglobin content now remained at a constant level of 80 per cent for 6 weeks, but then again decreased, thus calling for blood transfusions, but a longer intervals than prior to the operation.

Case 2. Sven Erik S., born March 3rd, 1945. Admitted to the Pediatric Clinic September 7th, 1945. There was no known history of blood disease in the family. He has two older siblings, both healthy. The patient was born one month prematurely. Birth weight 3 000 g. He has been entirely breast-fed. Growth and development have been normal, but since birth he has been very pale. The last couple of days prior to the admittance he was slack and pale, vomiting. Physical examination on admittance revealed a very exhausted child with waxen skin and mucous membranes. No visible jaundice. Marked craniotabes. Liver and spleen considerably enlarged. A faint systolic murmur was heard over the heart. Examination of the blood revealed the following data: Hemoglobin content 27 per cent, red blood count 1 350 000, colour index 1, white blood count 18 700, reticulocytes 45 per thousand, blood sedimentation rate 40 mm per hour, 9 nucleated red blood cells per 100 white. Bleeding time, coagulation time and prothrombin time were normal. Tibial puncture revealed a hyperplastic bone marrow, the red blood cells numbering 57 per cent of the total nucleated cells. Serum calcium 9.9 mg per cent, phosphorus 3.75 mg per cent, icterus index 17, Halo test 8.6 microns. Fragility test: Partial hemolysis at 0.52, total hemolysis at 0.36 per cent saline solution. Urine: Schlesinger's reaction was slightly positive in a 1 : 10 dilution. BWR was negative.

On account of the menacing situation other means were not attempted and we immediately started blood transfusions. The further course is illustrated in fig. 2. For two weeks the hemoglobin had a falling tendency, and it was difficult to keep a fairly constant hemoglobin level. Then a spontaneous increase was noted, the hemoglobin rising to 60 per cent during the following two weeks. From this time onwards, an aggravation set in, the hemoglobin content again decreasing. To prevent another serious, hemolytic crisis, a splenectomy was performed on October 6th, 1945 in the Surgical Departement A. In connection with the operation a total of 300 mls. blood was administered. Unfortunately he developed a postoperative pneumonia — resistant to Sulfathiazol and Penicillin — and he died three days after the operation. The removed spleen weighed 52 g (normal for the age is 12 g). Microscopically the trabeculae were slightly enlarged and fibrotic. The vascular walls appeared somewhat thickened. The sinusoids were distended and filled with blood. Some myelocytes were seen in the lymphoid tissue. Sparing pigment deposits.

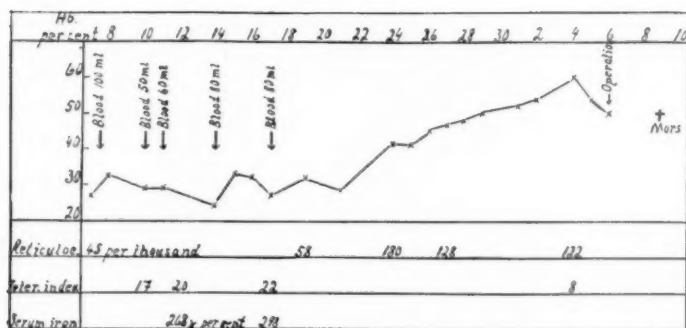


Fig. 2. Illustrating the course of the disease in case 2.

In a boy, half a year old, who had been pale since birth, a grave hemolytic anemia (Hb. 27 per cent) was diagnosed. After repeated blood transfusions a spontaneous improvement of the hemoglobin content was noted. A couple of weeks later signs of a hemolytic crisis recurred. Splenectomy was performed, but the patient died three days later from a postoperative pneumonia.

Comment.

Two children are concerned here, who have both been remarkably pale after birth with a yellowish tinge. A severe anemia with all signs of hemolysis has been ascertained at the age of 3 and 6 months respectively. Similar to ABT's cases, icterus is slightly pronounced in proportion to the marked hemolysis. In both cases the disease was running a chronic course with acute exacerbations.

When we are to discuss the diagnosis more closely, the question arises if our cases represent a rather serious manifestation of the familial, hemolytic icterus. Even MEULENGRACHT, in his monography on this disease (1918) has described one case in an infant who was waxen with a slightly yellowish tinge from the age of about 1 month. The hemoglobin content was as low as 10—15 per cent. The mother of the patient and four siblings suffered from the same disease. The child died 1 1/2 years old. LICHTENSTEIN has

reported a similar case. The patient was a boy in whom the first symptoms were noted at the age of 3 weeks. Hematological examination at the age of 7 years presented the typical picture of familial hemolytic icterus, though familial occurrence could not be demonstrated. At this age splenectomy was performed, and the boy was clinically cured. DEBRÉ and co-workers, also report on a serious case in a 4 month old child, whose mother suffered from the same disease. This child died shortly afterwards after having developed an otitis media. JOSEPHS mentions a case of severe, hemolytic anemia in an infant in whom a distinct icterus during the two first weeks of life was followed by a marked paleness. At the age of the 4 months the hemoglobin content was 34 per cent, and the red cell count 1 700 000. He does not mention any familial occurrence, and the morphology of the blood is not discussed more closely. Thus it is difficult to decide how to classify this case. ABT claims that also in his patients the disease was a specially serious manifestation of the familial, hemolytic icterus. However, certain characteristic features of this disease were absent in his case, namely the microcytosis, the spherocytosis and the decreased erythrocytic resistance to saline solution. Also from other quarters, however (STRANSKY, a. o.), it has been emphasized that normocytosis or macrocytosis and normal or slightly increased fragility of the erythrocytes are not incompatible with the diagnosis of familial, hemolytic icterus in early infancy. Typical and atypical forms are considered. But when no familial occurrence is found in addition to the atypical morphology of the blood and to the atypical course of the disease, in ABT's as well as in our cases, it may be indicated to revise the diagnosis. In both our cases the blood of the parents was examined closely. This revealed normal conditions with normal size of the erythrocytes, normal colour index and no increase of the reticulocytes. Thus, it may be justified to *indicate this condition as a separate disease differing from the familial, hemolytic icterus.*

The disease may be characterized as follows, therefore: A grave anemia present at birth or appearing during the first months of life, signs of hemolysis and a considerable increase of the reticulocytes, appearance of a varying number of nucleated red cells

in the peripheral blood, and an increased icterus index. The serum iron is considerably increased. A stained blood smear reveals erythrocytes of varying size, on an average slightly above normal estimated by the Halo test. The erythrocytic resistance to saline solution is normal or slightly decreased. In the bone marrow there is a constantly marked increase in the erythropoiesis with as much as 75 per cent of the nucleated cells belonging to the erythropoietic system. Liver and spleen are enlarged. The course is protracted and malignant, constantly associated with hemolysis, but with a certain tendency to remissions and exacerbations. In spite of the pronounced hemolysis icterus is only slightly pronounced. There is no familial occurrence of this disease.

In order to diagnose this condition the criteria mentioned above must be recognized at the same time as other forms of anemia must be excluded. Hemorrhage must be carefully searched for in order to exclude a hemorrhagic anemia which may cause a marked regeneration. Ovalocytosis, elliptocytosis, the LEDERER and the COOLEY types of anemia must be ruled out. When the infant is seen shortly after birth, the condition may be difficult to distinguish from erythroblastosis. The subsequent course and Rh determination will settle the matter.

As to the cause of this disease it is not possible to draw any conclusion from our present knowledge. The effect of the splenectomy indicates that the spleen plays a part pathogenetically. DAVID and MINOT, in a 4 $\frac{1}{2}$ month old boy suffering from a relapsing hemolytic anemia, during a crisis demonstrated hemolytic activity of the patient's serum against his own red blood cells and against blood cells from another patient with identical blood type. The boy was completely cured by splenectomy, and the hemolytic effect of his serum disappeared.

A condition to be considered is the marked craniotabes found in both our patients, but without any other sign of rickets. This might indicate that a larger part than normally of the cranium is monopolized in the blood formation, involving the substance of lamina interna and externa and thus rendering them more pliable.

Another sign of forced blood formation is the markedly pro-

truding tubera frontalia et parietalia with the depressed inter-jacent portion (caput quadratum, caput natiforme).

In the disease described all medication has proved ineffective. Repeated blood transfusions have been necessary to keep the patient alive. Splenectomy has been beneficial in two of ABT's cases. In one of our patients the operation caused a distinct change for the better. In cases with only temporary effect, this is belived to be due to a gradual development of accessory spleens re-establishing the blood-destructive function of the spleen. Accessory splenic tissue should be searched for, therefore, and removed at the operation. On account of the great disadvantage of the repeated blood transfusions, splenectomy is advisable. The hazard of the operation is considerably reduced when it is performed during a relatively quiet interval between crises, and it should preferably be postponed till after infancy.

Summary.

Two cases of severe, hemolytic anemia in infants are recorded. The blood findings and the course of the disease differed in several aspects from that of familial, hemolytic icterus. No similar cases were found in the family. Based on these cases and on others reported on in the literature it is suggested that this is a separate disease which must be distinguished from the familial, hemolytic icterus.

Résumé.

Deux cas d'anémie hemolytique sérieuse chez des enfants à la mamelle sont rapportés. L'état du sang ainsi que le cours de la maladie différaient sous plusieurs rapports de ceux d'un ictère hemolytique familial. Aucun cas similaire ne fut découvert dans la famille. En vue de ces cas et d'autres cas rapportés dans la littérature on est d'avis qu'il s'agit d'une maladie spéciale qui doit être distinguée de l'ictère hemolytique familial.

Zusammenfassung.

2 Fälle von schwerer haemolytischer Säuglingsanaemie, deren Befund und Verlauf von dem bei familiärem haemolytischem

Ikterus gewöhnlich vorkommenden abweicht. Es dürfte sich um eine besondere, von der letztgenannten verschiedene Krankheit handeln.

Resumen.

Se han registrado dos casos graves de anemia hemolítica entre niños. El análisis de la sangre y el curso de la enfermedad difirieron en varios aspectos de los de la ictericia hemolítica familiar. No se descubrió ningún caso similar en la familia. A base de estos casos y de otros relatados en la literatura médica se propone que ésta sea considerada una enfermedad diferente y que es necesario distinguirla de la ictericia hemolítica familiar.

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Des cas notés de troubles de conduite nerveux chez des élèves dans la période commençante d'un district scolaire de Göteborg.

Par

E. GEDDA.

On ne risque guère de se tromper en prétendant que l'intérêt pour les différents troubles nerveux, même assez légers, chez les enfants augmente toujours chez les instituteurs, les médecins scolaires, le grand public. On a commencé à se rendre compte que ces troubles doivent être souvent la cause de troubles de la conduite et de difficultés à l'école, ainsi que présage de futures maladies nerveuses chez les adultes et par conséquent qu'ils sont d'une très grande importance.

Pour avoir une idée de la fréquence de ces troubles de la conduite dont les parents et les instituteurs se sont inquiétés et qui ont été observés chez les élèves commençants de Göteborg par le médecin scolaire j'ai parcouru les cartes de santé des commençants déjà examinées les années scolaires 1945—46 et 1946—47 dans les districts scolaires dont j'ai la charge. Le district qui compte environs 3 000 enfants a été divisé en trois parties, A, B et C. La catégorie A se compose à peu près totalement de la classe ouvrière, comprenant un grand nombre de familles nombreuses et qui habitent souvent des maisons cooperatives subventionnées. La catégorie C est d'une espèce semblable mais un peu moins prononcée, tandis que la catégorie B représente le faubourg, habité par la bourgeoisie aisée.

Tableaux 1. Il est bien clair que la méthode même de prendre les renseignements préparatoires est d'une très grande importance. Pendant les examens médicaux on peut, par la voie

Tableau 1.

Des cas notés de troubles de conduite nerveux chez des enfants à l'école dans la période commençante d'un district scolaire de Gothembourg.

| Les indications primaires du | nombre de cas | pour cent de toute la matière (879) |
|---------------------------------------|---------------|-------------------------------------|
| 1) correspondant, par écrit | 115 | 13.08 ± 1.29 |
| 2) " oralement simplement | 179 | 20.36 ± 1.84 |
| 3) professeur, seulement | 77 | 8.76 ± 0.91 |
| 4) médecin, seulement | 20 | 2.28 ± 0.25 |
| En somme | 391 | 44.48 ± 2.81 |

directe, constater seulement un très petit nombre de ces troubles de la conduite tant que l'on n'a pas des renseignements anamnestiques. D'un autre côté, cependant, on peut distinguer la plupart de ces troubles de la conduite rien que par un examen médical des maladies physiques et ainsi les diagnostiquer. Les cas que le médecin seul découvre à la visite médicale même, sont relativement rares dans cet examen 2.3 % des 879 enfants que l'examen comprend. Mais le diagnostic de trouble psychoneurotique de conduite dans tous les autres cas, rapportés par les professeurs ou par les parents ne peut être regardé comme vérifié que dans le cas où l'examen médical a prouvé qu'on n'a pas affaire à une maladie organique ou en tout cas que cette maladie n'est pas le point important.

Avant, ou juste au commencement des études, on remet aux parents des commençants dans les écoles primaires de Göteborg un questionnaire sur l'état de santé de l'enfant et de la famille. Par ce questionnaire, 115 des 879 parents, c'est-à-dire 13 %, se sont plaints de troubles psychoneurotiques de conduite chez les enfants. Considérablement plus — ou 179 (20.4 % de la matière totale) n'ont présenté à l'école leurs soucis qu'oralement aux examens médicaux, ce qui témoigne de l'importance du fait que les parents ont accès à ces examens. Il est à remarquer qu'aucun d'eux n'a été directement interrogé sur des troubles psychoneurotiques de conduite chez les enfants. Les faits se

sont révélés en réponse à une question posée à tous les parents, et conçue littéralement de la même manière: Trouvez-vous cet enfant en bonne santé où en santé délicate? Outre les enfants dont les parents ont déclaré qu'ils ont des troubles neurotiques, l'institutrice en a rapporté encore à un pourcentage de 9. Ce rapport est le résultat d'un appel toujours pareil à chaque institutrice *avant* l'examen médical de la classe, pour faire savoir au médecin scolaire (dans les cas convenables aussitôt avant ou après l'examen médical des enfants en question), si l'enfant présente quelque écart important dans sa manière de travailler ou dans sa manière de se conduire, comme p. e. des intermittances ou des tensions, une vivacité dérangeante, des fautes de prononciation, s'ils sont à la garde des assistantes sociales ou du conseil de surveillance.

Le tableau démontre que, des 879 enfants que l'examen comprend, 391 enfants (c. a d. 44.5 %) présentent des troubles nerveux. Il s'agit ici de tous les commençants du district de Örgryte à Gothenbourg pendant deux années scolaires (1945 et 1946) sauf deux ou trois classes, installées dans une petite école éloignée, ainsi que quelques classes, appartenant du point de vue géographique à un autre district, mais transmises pour certaines raisons au district de Örgryte.

Le tableau 2 indique les divers formes de changement dans la conduite et aussi le pourcentage de ces formes, comparées à l'ensemble. Quant à toutes les rubriques j'ai dû les formuler dans ces tableaux aussi sommairement que possible.

Grâce aux réponses assez détaillées des parents, rendues en général littéralement dans les cartes de santé, on a, bien entendu, une image beaucoup plus vive de l'état de l'enfant, témoignant en général d'un état de choses souvent pas du tout négligeable. En outre, on a trouvé souvent chez un enfant nerveux en même temps plusieurs de ces troubles notés dans le tableau. Chez les 391 enfants qui constituent «les sujets neurotiques» on ne trouvera pas moins de 598 cas des 15 groupes différents que le tableau nous offre.

Comme troubles nerveux de l'estomac et des intestins on a noté: colique ombilicale, vomissements matinaux avant le de-

Tableau 2.

Des sortes différentes de troubles de conduite nerveux chez des enfants
cent de toute la

| | Nervosité Sensibilité Suscepti- bilité | Difficultés de con- centration. Reve de jour | Ambition exagérée Inhibi- tion | Inquié- tude Peur Angoisse | Bégaie- ment | Tics |
|---|---|--|---|-------------------------------------|-----------------|----------------|
| En nombre absolu . | 169 | 23 | 12 | 31 | 18 | 13 |
| En pour cent de toute la matière | 19.23 ± 1.77 | 2.62 ± 0.29 | 1.37 ± 0.15 | 3.58 ± 0.39 | 2.05 ± 0.23 | 1.48 ± 0.17 |

part de l'enfant pour l'école, réflexe gastrocolique-pathologique, encopræsis; comme dérangements de sommeil: somnambulisme, cris pendant la nuit, grandes difficultés de s'endormir. Comme difficultés morales d'adaption j'ai découvert ici celles qui entraînent des conflits avec la famille et l'école, ou autrement, notamment: désobéissance, entêtement, obstination, absence injustifiée, mauvaise conduite, habitude de mentir, habitude de chiper, dissolution, ce qu'on peut appeler tout court et d'une façon plus réaliste: des mauvaises habitudes (délinquency).

Le tableau 3 donne la distribution des sexes des sujets et il nous montre que les garçons sont plus nombreux parmi les élèves neurotiques qu'entre les autres. La différence est 6 ± 3.4 %, offrant ainsi un écart vraisemblable du point de vue statistique, mais pas tout à fait sûr.

Tableau 3.

Répartition de sexe dans les parties différentes du district.

| La matière nerveuse | | | Les autres | | | Toute la matière | | |
|---------------------|--------|-------|------------|--------|-------|------------------|--------|-------|
| Garçons | Filles | Total | Garçons | Filles | Total | Garçons | Filles | Total |
| 207 | 184 | 391 | 229 | 259 | 488 | 436 | 443 | 879 |

Garçon = $52.94 \% \pm 2.52$ Garçon = $46.98 \% \pm 2.26$
Différence 6.01 ± 3.39 %.

2.

d'école dans la période commençante en nombre absolu et en pour matière (879).

| Mouvements nerveux (gênant) | Ongles rongés | La suçage du ponce | Anorexie nerveuse | Dérangement nerveux de l'estomac et d'intestins (desquels encopresis) | Enuresis | Troubles du sommeil | Névroses des organes | Difficultés morales d'adaptation |
|-----------------------------|---------------|--------------------|-------------------|---|----------|---------------------|----------------------|----------------------------------|
| 68 | 59 | 14 | 66 | 22 (2) | 32 | 35 | 4 | 32 |
| 7.74 | 6.71 | 1.59 | 7.51 | 2.50 | 3.64 | 3.98 | 0.46 | 3.64 |
| ± 0.81 | ± 0.71 | ± 0.18 | ± 0.79 | ± 0.28 | ± 0.40 | ± 0.43 | ± 0.05 | ± 0.40 |

Le tableau 4 nous montre le nombre des enfants uniques et «des autres enfants isolés». Cette dernière dénomination indique le premier ou le dernier enfant d'un cercle de frères et sœurs, si l'intervalle d'âge entre cet enfant et son prédécesseur ou son successeur est de plus de 3 ans. J'ai choisi cet intervalle en me basant sur les expériences que déjà à cet intervalle d'âge de 3 ans un certain caractère, propre à l'enfant unique, commence à se manifester chez certains enfants. Selon ce tableau l'augmentation de la natalité qui caractérise en ces derniers temps notre population a eu pour résultat qu'à Göteborg, en 1938, l'enfant unique à la période d'entrée représente aujourd'hui un pourcentage de 18 seulement, comparé à 30 % de la période préscolaire et 20 % de la période scolaire (montré par une recherche sur les sujets de jardins d'enfants et d'écoles primaires de la dite année). La partie B, type classe moyenne, offre maintenant même un pourcentage de 14 seulement, quant à l'enfant unique, ce qui laisse comprendre que ces classes fortunées — même si elles étaient autrefois à la tête de la dénatalité — sont maintenant les premières quant il s'agit d'une augmentation de natalité.

Ce tableau a beaucoup étonné l'auteur en montrant que la prédominance de l'enfant unique parmi les sujets neurotique est tellement faible qu'on ne peut pas la vérifier du point de vue statistique. «Les autres enfants isolés» sont même plus fréquents

Tableau 4.

Les conditions des

Des enfants isolés = l'enfant premier ou dernier si l'intervalle au

| Dis- trict | La matière nerveuse | | | | | | | | Les | | | |
|---------------|---------------------|------------|-------------------|-------|--------|-------|-------|-------|--------------------|------------|-------------------|-------|
| | Enfants uniques | | Enfants isolés | | Autres | | Total | | Enfants uniques | | Enfants isolés | |
| | abs. | % | abs. | % | abs. | % | abs. | % | abs. | % | abs. | % |
| A | 36 | 25.00 | 24 | 16.67 | 84 | 58.33 | 144 | 42.60 | 38 | 19.59 | 54 | 27.84 |
| B | 17 | 15.60 | 33 | 30.28 | 59 | 54.13 | 109 | 43.95 | 18 | 12.95 | 38 | 27.34 |
| C | 25 | 18.12 | 34 | 24.64 | 79 | 57.25 | 138 | 47.10 | 29 | 18.71 | 45 | 29.00 |
| | 78 | 19.95 | 91 | 23.27 | 222 | 56.78 | 391 | 44.48 | 85 | 17.42 | 137 | 28.67 |
| | | ± 2.02 | | | | | | | | ± 1.72 | | |

La différence entre le nombre d'enfants seuls dans la matière nerveuse et dans les autres = 2.58 ± 2.65 .

∴ pas de différence démontrable dans cette matière.

1938 — 30 % des enfants seuls entre les enfants d'âge préscolaire.
et 20 % " " " " les élèves des écoles.

encore parmi les sujets normaux que parmi les sujets neurotiques.

Il se peut bien que ce résultat, qui diffère si nettement des expériences qu'a fait chaque médecin d'enfant, soit en partie apparent. On ose peut-être présumer que les parents de cet enfant unique répugnent à porter un jugement qui puisse être compris comme une critique de leur petit chéri. Ce soupçon me semble vérifié par le tableau 8. Ces parents regardent évidemment comme remarquables seulement les symptômes très marquants, et dans ces conditions il ne s'agit ici que de quelques cas isolés, qui prédominent en quelque sorte. L'anamnèse devient ainsi plus monosymptomatique. On pourrait dire, cependant, que — si on voit le problème neurotique en grand — l'enfant unique et «l'enfant isolé» a eu, par le tableau 4, une sorte de satisfaction. Si l'on étudie, d'autre part, les différents formes neurotiques isolés — ce que nous allons faire tout à l'heure à propos du tableau 8 — nous trouverons que certains des symptômes donnés dominent cependant chez «l'enfant soigné à l'excès».

frères et soeurs.

frère et soeur qui sont les prochains en âge est plus que 3 ans.

| autres | | | | Toute la matière | | | | | | | |
|--------|-------|-------|-------|--------------------|-------|-------------------|-------|--------|-------|-------|--------|
| Autres | | Total | | Enfants uniques | | Enfants isolés | | Autres | | Total | |
| abs. | % | abs. | % | abs. | % | abs. | % | abs. | % | abs. | % |
| 102 | 52.58 | 194 | 57.40 | 74 | 21.89 | 78 | 23.08 | 186 | 55.03 | 338 | 38.45 |
| 83 | 59.71 | 139 | 56.05 | 35 | 14.11 | 71 | 28.63 | 142 | 57.26 | 248 | 28.21 |
| 81 | 52.26 | 155 | 52.90 | 54 | 18.43 | 79 | 26.96 | 160 | 54.61 | 293 | 33.34 |
| 266 | 54.51 | 488 | 55.52 | 163 | 18.54 | 228 | 25.94 | 488 | 55.52 | 879 | 100.00 |

Le tableau 5 est une tentative d'étudier les relations eventuelles de la constitution avec des troubles de conduite psychoneurotique. Dans le chéma des examens de classe des écoles primaires à Göteborg une colonne se trouve déjà dans tous les cas pour spécifier si la constitution est typiquement trapu ou mince. Ceux-ci devraient correspondre aux constitutions «pycniques» ou «astheniques» selon Kretschmer. On discute la possibilité de fixer chez les enfants ces types de constitution. Ce qui certain est c'est que le médecin peut, dans une classe, bien voir que certains enfants se distinguent de la plupart par une constitution typiquement mince ou trapue. On n'arrive pas, bien entendu, à obtenir des limites marquées par cette méthode somatoscopique, mais cela ne me semble pas être nécessaire pour cette fin. En déterminant le type je n'ai pas du tout tenu compte des symptômes nerveux, dont la relation avec le type m'était inconnue. Selon le tableau les élèves sveltes sont les plus fréquents parmi les sujets névrotiques, et les élèves trapus les plus fréquents parmi les sujets de contrôle. Les différences, dans les deux cas à un pourcentage de presque 7, sont, en ce qui concerne les types trapus, presque 3, et quant au types sveltes bel et bien deux fois leurs erreurs moyennes. Ces différences sont ainsi du point de vue statistique certaines, ou bien extrêmement vraisemblables.

Tableau 5.
La type physique.

| Type | La matière nerveuse | | Les autres | | Toute la matière | |
|-------------|---------------------|--------------------------------|-------------|--------------------------------|------------------|------------------|
| | Nom- bre | Pourcentage | Nom- bre | Pourcentage | Nom- bre | Pourcen- tage |
| Ramassés . | 69 | $17.65 \pm 1.93 (\sqrt{3.72})$ | 119 | $24.39 \pm 1.94 (\sqrt{3.78})$ | 188 | 21.39 |
| Sveltes . . | 131 | $33.50 \pm 2.89 (\sqrt{5.70})$ | 130 | $26.64 \pm 2.00 (\sqrt{4.00})$ | 261 | 29.69 |
| Ordinaire . | 191 | 48.85 | 239 | 48.97 | 430 | 48.92 |
| | 391 | 100.00 | 488 | 100.00 | 879 | 100.00 |

La différence entre les ramassés de la matière nerveuse et les mêmes parmi les autres = 6.74 ± 2.74 %.

Et la différence entre les sveltes de la matière nerveuse et les mêmes parmi les autres = 6.88 ± 3.11 %.

∴ il y a de grandes chances pour que les ramassés sont moins nombreux et les sveltes sont plus dans la matière nerveuse que dans les autres.

Tableaux 6. Souvent on a voulu trouver chez l'enfant nerveux certains traits extérieurs — des cils longs, des yeux cernés une physionomie de spleen et d'ennui, lingua geografica et des cheveux lanugineux. Wallgren a nommé ce type «le type neuro-labile». Par intérêt pour ses choses-là j'ai aussi l'habitude de noter sur les cartes de santé ces marques distinctives. Chez les sujets neurotiques ce type est cependant encore plus fréquent, c'est ici à un pourcentage de 39.4 comparé aux autres avec 27.3 La différence 12.14 ± 3.19 est certaine du point de vue statistique.

Il me semble en outre, que le type neurolabile est plus fréquent chez les garçons que chez les jeunes filles (la différence est 6.66 ± 3.16 %). Ce type est plus fréquent chez les enfants sveltes que chez les enfants trapus (la différence 7.67 ± 4.5 %). Il est plus fréquent chez l'enfant unique que chez les autres mais surtout le plus fréquent chez l'enfant isolé (la différence vis-à-vis des autres est 8.89 ± 3.8 ce qui semble indiquer de toute évidence que le type neurolabile est — du moins à en certain degré — un produit du milieu quand, d'un autre côté, les types Kretschmer semblent être héréditaires. Ce type neurolabile, enfin, est un peu plus

Tableau 6.
Le nombre d'un type neurolabil
divisé de

| | dans la matière nerveuse | de là d'un type neur. | % | dans la mat. restante | de là d'un type neur. | % | dans toute la matière | de là d'un type neur. | % | Diff. |
|---|--------------------------------|-----------------------------|-------------------------|-----------------------------|-----------------------------|-------------------------|-----------------------------|-----------------------------|--------------------------|-----------------|
| I. Sexe | | | | | | | | | | |
| Garçons . . . | 207 | 84 | 40.58 | 229 | 73 | 31.88 | 436 | 157 | $36.01 \pm \sqrt{5.29}$ | 6.66 ± 3.16 |
| J. filles . . . | 184 | 70 | 38.04 | 259 | 60 | 23.17 | 443 | 130 | $29.85 \pm \sqrt{4.68}$ | |
| II. Type | | | | | | | | | | |
| Ramassés . . | 69 | 30 | 43.48 | 119 | 37 | 31.09 | 188 | 67 | $35.64 \pm \sqrt{12.20}$ | 7.67 ± 4.5 |
| Sveltes . . . | 131 | 46 | 35.11 | 130 | 27 | 20.77 | 261 | 73 | $27.97 \pm \sqrt{8.04}$ | |
| Ordin. . . . | 191 | 78 | 40.84 | 239 | 69 | 28.87 | 430 | 147 | 34.19 | |
| III. Les conditions des frères et sœurs | | | | | | | | | | |
| Enfants unique | 78 | 30 | 38.46 | 85 | 24 | 28.24 | 163 | 54 | 33.18 | |
| Autres enf. isol. | 91 | 44 | 48.35 | 137 | 44 | 32.12 | 228 | 88 | $38.60 \pm \sqrt{10.39}$ | 8.89 ± 3.8 |
| Restants . . . | 222 | 80 | 36.04 | 266 | 65 | 24.44 | 488 | 145 | $29.71 \pm \sqrt{4.28}$ | |
| IV. La position sociale du correspondant | | | | | | | | | | |
| Professions des manchettes . | 138 | 61 | 44.20 | 189 | 53 | 28.04 | 327 | 114 | 34.86 | |
| Autres . . . | 253 | 93 | 36.76 | 299 | 80 | 26.76 | 552 | 173 | 31.34 | |
| | 391 | 154 | $39.39 \pm \sqrt{6.11}$ | 488 | 133 | $27.25 \pm \sqrt{4.06}$ | 879 | 287 | 32.65 | |

Diff 12.14 \pm 3.19

fréquent chez les enfants des familles un peu fortunées (où le père de famille a une profession de manchette) que chez les autres enfants de ce sujet, une différence plus marquée dans le sujet neurotique que dans les autres sujets.

Tableau 7.

La position sociale du correspondant

(division approximative en professions des manchettes — m —
et en autres)

| District | La matière nerveuse | | | | | | Restants | | | | | | Toute la matière | | | | | |
|----------|---------------------|-----------------|----------|-------|-------|-------|----------|-----------------|----------|-------|-------|-------|------------------|-------|----------|-------|-------|-------|
| | m | | Restants | | Total | | m | | Restants | | Total | | m | | Restants | | Total | |
| | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % |
| A | 18 | | 126 | | 144 | | 32 | | 162 | | 194 | | 50 | 14.79 | 288 | 85.21 | 338 | 38.6 |
| B | 92 | | 17 | | 109 | | 125 | | 14 | | 139 | | 217 | 87.50 | 31 | 12.50 | 248 | 28.2 |
| C | 28 | | 110 | | 138 | | 32 | | 123 | | 155 | | 60 | 20.48 | 233 | 79.52 | 293 | 33.3 |
| | 138 | 35.29 ± 2.42 | 253 | 64.71 | 391 | 44.48 | 189 | 38.73 ± 2.25 | 299 | 61.27 | 488 | 55.52 | 327 | 37.20 | 552 | 62.80 | 879 | 100.0 |

La différence entre les professions des manchettes de la matière nerveuse et des autres est 3.44 ± 3.27 — ainsi en cette matière personne.

Le tableau 7 nous montre les rapports entre le standard social des enfants et les troubles psychoneurotiques. Le classement des pères dans les professions de manchettes et les autres professions a été fait selon les méthodes généralement admises. Quant aux professions de manchettes des pères j'ai trouvé un pourcentage de 87.5 dans la partie B du district mais seulement 14.8 dans la partie A et 20.5 dans la partie C, ce qui correspond bien avec les différents caractères des diverses parties, déjà signalées au commencement de cet exposé. Le sujet neurotique offre un pourcentage de 35.5 pour les pères de profession de manchettes et 38.8 pour les autres professions. La différence ici cependant, qu'elle est si peu importante (3.44 ± 3.3) peut être due au hasard.

Enfin, j'ai fait dans le tableau 8 le partage des différents symptômes neurotiques en rapport avec le sexe, le type consti-

tutionnel les rapports entre frères et sœurs, les conditions sociales des parents.

Les garçons, qui ont 78 symptômes neurotiques sur cent individus (comparés aux filles avec 58) dominent surtout quant aux difficultés de concentration, peur et angoisse, bégaiement, tics, mouvements nerveux, rongement des ongles, neuroses des organes. Il s'agit surtout de l'agilité et du tempérament et doit se rapporter à la plus grande agilité du sexe mâle de la période uniclululaire. Les jouissances paisibles et peu agressives de sucer son doigt domine d'autre part chez les jeunes filles.

Quant au type constitutionnel les enfants sveltes offrent 79 symptômes sur cent individus, mais les trapus seulement 48. Ces derniers prédominent seulement quant il s'agit d'ambition exagérée, inhibition et tension, tics, troubles du sommeil. Le type pycnique désirant dans ses périodes d'activité aller au-dessus de ses forces, tombe rapidement, quand il ne réussit pas, dans un état d'inhibition et de mélancolie, chose qui est bien compréhensible. Des types vifs qui, étant dans un état de timidité, donnent des signes de tics, doivent compter peut-être parmi les types pycniques tandis que leur tendance à des troubles du sommeil doit être attribué à la vive imagination.

Aussi les enfants trapus ont bien moins de symptômes neurotiques que les enfants ordinaires. Les proportions sont ici 48—70.

Nous avons déjà vu dans notre discussion du tableau 4 — que l'enfant unique et, mieux encore «l'enfant isolé» est mieux placé que les autres enfants quant au nombre des symptômes déjà notés (67.6 respectivement 72 pour 100 individus). Cela peut s'expliquer peut-être par le fait que les parents de l'enfant unique et «de l'enfant isolé» ont plus d'indulgence pour les troubles de conduite légers de leurs enfants. C'est seulement les plus grands troubles qui sont indiqués. L'anamnèse devient par conséquence plus monosymptomatique. En outre on peut voir d'après cette partie du tableau que la nervosité, combinée à une sensibilité remarquable, est assez peu prominente chez cet enfant unique ou autrement isolé. Les difficultés de concentration et les rêves de jour sont typiques pour l'enfant vraiment unique, mais cela n'est

Tableau 8. Des sortes différentes de névrose divisées.

| | Nervosité | | Difficultés de concentration | | Ambition exagérée Inhibition | | P'eur | | Bégaïement | | Tics | | Mouvement nerveux | | Ongles rongés | |
|---|-----------|-------------------------|------------------------------|------------------------|------------------------------|------|-------|------|------------|------------------------|------|------|-------------------|-------------------------|---------------|------------------------|
| | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % |
| I) de sexe (pourcentage de garçons resp. jeunes filles de toute la matière) | | | | | | | | | | | | | | | | |
| Garçons . | 87 | 19.95 | 19 | $4.35 \pm \sqrt{0.95}$ | 7 | 1.60 | 18 | 4.13 | 14 | $3.21 \pm \sqrt{0.71}$ | 9 | 2.06 | 50 | $11.46 \pm \sqrt{2.33}$ | 38 | $8.71 \pm \sqrt{1.82}$ |
| Filles . . | 82 | 18.51 | 4 | $0.90 \pm \sqrt{0.20}$ | 5 | 1.13 | 13 | 2.93 | 4 | $0.90 \pm \sqrt{0.20}$ | 4 | 0.90 | 18 | $4.06 \pm \sqrt{0.88}$ | 21 | $4.74 \pm \sqrt{1.02}$ |
| Diff. . . | | | | 3.45 ± 1.07 | | | | | | 2.31 ± 0.95 | | | | 7.40 ± 1.79 | | 3.97 ± 1.69 |
| II) de type physique (pourcentage de tous de la même type de toute la matière) | | | | | | | | | | | | | | | | |
| Ramassés | 23 | $12.23 \pm \sqrt{5.71}$ | 1 | $0.53 \pm \sqrt{0.28}$ | 4 | 2.13 | 5 | 2.64 | 1 | 0.53 | 4 | 2.13 | 12 | 6.38 | 6 | $3.19 \pm \sqrt{1.63}$ |
| Sveltes . | 61 | $23.37 \pm \sqrt{6.86}$ | 10 | $3.88 \pm \sqrt{1.41}$ | 3 | 1.15 | 14 | 5.36 | 7 | 2.68 | 4 | 1.53 | 14 | 5.86 | 21 | $8.05 \pm \sqrt{2.84}$ |
| Ordin. . . | 85 | 19.77 | 12 | 2.79 | 5 | 1.16 | 12 | 2.79 | 10 | 2.32 | 5 | 1.16 | 42 | 9.77 | 32 | 7.44 |
| Diff. . . | | 11.14 ± 3.54 | | 3.30 ± 1.30 | | | | | | | | | | | | 4.86 ± 2.11 |
| III) de conditions des frères et sœurs (pourcentage de toutes les mêmes conditions de toute la matière) | | | | | | | | | | | | | | | | |
| Enfants uniques | 30 | 18.4 | 7 | $4.29 \pm \sqrt{2.52}$ | 2 | 1.23 | 4 | 2.45 | 1 | 0.61 | 3 | 1.84 | 11 | 6.75 | 8 | 4.91 |
| Autres enf. isol. | 39 | 17.11 | 2 | $0.88 \pm \sqrt{0.38}$ | 4 | 1.75 | 10 | 4.39 | 2 | 0.88 | 1 | 0.44 | 14 | 6.14 | 15 | 6.58 |
| Restants . | 100 | 20.49 | 14 | 2.87 | 6 | 1.23 | 17 | 3.48 | 15 | 3.07 | 9 | 1.84 | 43 | 8.81 | 36 | 7.38 |
| Diff. . . | | | | 3.41 ± 1.70 | | | | | | | | | | | | |
| IV) de position sociale (pourcentage de tous des mêmes conditions de toute la matière) | | | | | | | | | | | | | | | | |
| Prof. des manchettes | 61 | 18.65 | 6 | 1.58 | 5 | 1.53 | 9 | 2.75 | 7 | 2.14 | 8 | 2.45 | 22 | 6.73 | 26 | 7.95 |
| Autres . . | 108 | 19.57 | 17 | 3.98 | 7 | 1.27 | 22 | 3.99 | 11 | 1.99 | 5 | 0.91 | 46 | 8.33 | 33 | 5.98 |
| Diff. . . | | | | | | | | | | | | | | | | |
| | 169 | 19.23 | 23 | 2.62 | 12 | 1.37 | 31 | 3.53 | 18 | 2.05 | 13 | 1.48 | 68 | 7.74 | 59 | 6.71 |

Tableau 8 (continuation).

| | La suçage de ponce | | Anorexie nerveuse | | Dérangement de l'estomac et des intestins | | Enuresis | | Troubles du sommeil | | Névroses des organes | | Difficultés morales d'adaptation | | Des sortes névroses | |
|---|--------------------|------------------------|-------------------|-------------------------|---|------|-----------------|------------------------|---------------------|------------------------|----------------------|------|----------------------------------|------------------------|---------------------|--------------------------|
| | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | abs | % | Tot. | Sur cent individus suiv. |
| I) de sexe (pourcentage de garçons resp. jeunes filles de toute la matière) | | | | | | | | | | | | | | | | |
| Garçons . | 4 | $0.91 \pm \sqrt{0.21}$ | 27 | 6.19 | 10 (2) | 2.29 | 14 | 3.21 | 21 | 4.82 | 3 | 0.69 | 18 | 4.13 | 339 | 436 |
| Filles . | 10 | $2.26 \pm \sqrt{0.49}$ | 39 | 8.80 | 12 | 2.71 | 18 | 4.06 | 14 | 3.16 | 1 | 0.23 | 14 | 3.16 | 259 | 443 |
| Diff. . | | 1.39 ± 0.83 | | | | | | | | | | | | | | 58 |
| II) de type physique (pourcentage de tous de la même type de toute la matière) | | | | | | | | | | | | | | | | |
| Ramassés | 2 | 1.06 | 10 | $5.82 \pm \sqrt{2.68}$ | 1 | 0.53 | 7 | 3.72 | 10 | 5.82 | 0 | 0 | 4 | 2.13 | 90 | 188 |
| Sveltes . | 6 | 2.80 | 28 | $10.78 \pm \sqrt{3.67}$ | 3 | 1.15 | 12 | 4.60 | 8 | 3.66 | 1 | 0.38 | 13 | 4.98 | 205 | 261 |
| Ordin. . | 6 | 1.40 | 28 | 6.51 | 18 (2) | 4.19 | 13 | 3.92 | 17 | 3.95 | 3 | 0.70 | 15 | 3.49 | 303 | 430 |
| Diff. . | | | | 5.41 ± 2.52 | | | | | | | | | | | | 70 |
| III) de conditions des frères et sœurs (pourcentage de toutes les mêmes conditions de toute la matière) | | | | | | | | | | | | | | | | |
| Enfants uniques | 0 | 0 | 16 | $9.82 \pm \sqrt{5.43}$ | 4 (1) | 2.45 | 3 | $1.84 \pm \sqrt{1.11}$ | 14 | $8.59 \pm \sqrt{4.82}$ | 2 | 1.23 | 4 | $2.45 \pm \sqrt{1.47}$ | 109 | 163 |
| Autres enf. isol. | 6 | 2.63 | 18 | 7.89 | 5 | 2.19 | 13 | $5.70 \pm \sqrt{2.36}$ | 4 | $1.75 \pm \sqrt{0.75}$ | 0 | 0 | 7 | 3.07 | 140 | 228 |
| Restants . | 8 | 1.64 | 32 | $6.56 \pm \sqrt{1.26}$ | 13 (1) | 2.66 | 16 | 3.38 | 17 | 3.48 | 2 | 0.41 | 21 | $4.30 \pm \sqrt{0.84}$ | 349 | 488 |
| Diff. . | | | | 3.36 ± 2.59 | | | 3.56 ± 1.86 | | 6.84 ± 2.86 | | | | | 1.85 ± 1.52 | | |
| IV) de position sociale (pourcentage de tous des mêmes conditions de toute la matière) | | | | | | | | | | | | | | | | |
| Prof. des manchettes | 9 | 2.75 | 18 | 5.50 | 6 | 1.58 | 12 | 3.67 | 9 | 2.75 | 2 | 0.61 | 8 | $2.45 \pm \sqrt{0.78}$ | 208 | 327 |
| Autres . | 5 | 0.91 | 48 | 8.70 | 16 (2) | 2.90 | 20 | 3.62 | 26 | 4.71 | 2 | 0.36 | 24 | $4.35 \pm \sqrt{0.75}$ | 390 | 552 |
| Diff. . | | | | | | | | | | | | | | 1.90 ± 1.23 | | 71 |
| | 14 | 1.59 | 66 | 7.51 | 22 (2) | 2.50 | 32 | 3.64 | 35 | 3.98 | 4 | 0.46 | 32 | 3.64 | 598 | 879 |

Diff. de la nervosité entre les sveltes et les ramassés 11.14 ± 3.54 .

pas le cas chez «l'enfant isolé» très occupé aussi par ses frères et sœurs. Le fait que le bégaiement soit peu commun chez l'enfant unique et chez l'enfant isolé peut indiquer, je crois, qu'il se produit plus facilement quand l'éducation est trop sévère. L'enfant né sur le tard, exposé aux admirations des parents et des frères et sœurs, ne doit pas avoir tendance à montrer des réactions de timidité, comme par exemple des tics. Il est bien difficile d'expliquer, d'autre part, pourquoi l'enfant isolé suce son doigt tandis que l'enfant unique le fait si rarement. On pourrait, si cette différence dépend d'autre facteur que du hasard, proposer beaucoup d'explications, qui resteraient cependant toujours des suppositions. On a prétendu que la succion des doigts devait être le résultat d'un sevrage trop rapide et précipité. Il est bien possible, par exemple, que les seins de la mère, qui, maintenant, n'est pas très jeune, cessent trop tôt de donner du lait. C'est peut-être seulement une chose de l'âge, mais il peut aussi être à dessein. Ayant des expériences quant à l'allaitement des enfants plus âgés elle croit pouvoir négliger un peu les prescriptions médicales du sevrage. Les parents, ainsi que les frères et sœurs, sont disposés à dorloter beaucoup le petit enfant, né sur le tard et il est bien possible qu'ils commencent à lui donner à manger à la cuiller de très bonne heure. Cette hypothèse peut se vérifier seulement par un recherche qui montre avec une certitude statistique que les enfants nés sur le tard sont sevrés plus tôt que les autres enfants.¹

Il est aussi très possible que l'enfant en queue est longtemps retenu dans une phase peu développée précisément parce que les parents et les frères et sœurs le dorlotent tellement.

L'anorexie nerveuse a été nommé parfois la maladie de l'enfant unique. Cela se confirme aussi par les chiffres qui nous donnent un pourcentage de presque 10. Chez l'enfant isolé nous trouvons le pourcentage 8. L'enuresis, peu fréquent chez l'enfant unique, est d'autant plus fréquent chez l'enfant isolé. Par conséquent, on ne doit pas le soupçonner ici, puisque toutes ces deux catégories doivent être regardées comme trop soignées. Il faudrait plutôt con-

¹ G. HERLITZ (Acta Pæd. I. VII. 1947) a nouvellement fait voir, que la mère plus vieille commence le sevrage plus tôt que la mère plus jeune (ici important), bien qu' ensuite elle contient l'aliment mixte plus prolongé.

sidérer l'attitude affectée des sœurs vis-à-vis de l'enfant en queue: attitude qui entrave le développement de la personnalité. Il faut remarquer ici que la succion des doigts ainsi que l'enuresis sont des preuves d'un retard et que l'enfant reste dans une phase primitive, une inhibition de quelque sorte. Ici un manque de confiance en soi-même doit plus tard jouer un rôle important. L'enfant unique, qui a souvent des qualités de chef et de conducteur très marquées n'a pas de disposition pour ce manque de confiance en soi-même, mais «l'enfant isolé» peut bien l'acquérir vis-à-vis de ses frères et sœurs aînés. Le premier enfant né longtemps avant les autres enfants, se comporte naturellement comme l'enfant unique dans le cas ici mentionné et doit être placé avec celui-ci. L'enfant unique domine aussi considérablement parmi les troubles de sommeil. Il semble que l'absence de frères et sœurs contribue beaucoup à produire la peur de l'obscurité sous des formes différentes aussi qu'une augmentation de cet introspection qui a l'habitude de se rapporter aux notions hypocondriques. A la première année à l'école primaire l'enfant unique et l'enfant isolé sont rares en ce qui concerne les mauvaises habitudes, toutefois à un tel degré, que leurs parents, qui doivent être très indulgents, ont toutes les raisons de se plaindre. Un examen médical éventuel à la follow-up doit montrer si cet état de choses restera aussi plus tard.

Il semble que la position sociale de la famille n'ait aucune influence remarquable sur les cas de neuroses si ces derniers sont donnés spécialement dans les rapports des parents. Déjà le tableau 7 nous le montre en ce qui concerne les individus. S'il s'agit de symptômes neurotiques, les relations sont 64 sur 100 individus avec des pères appartenant à la profession de manchettes contre 71 pour les autres. Les difficultés de concentration, la peur et les mauvaises habitudes sont moins marquées chez eux que chez les autres, tandis que le bégaiement et les tics prédominent dans les familles plus aisées. Il semble aussi que succion des doigts et rongement des ongles soient plus fréquents ou du moins plus observées dans ces familles.

Quant à l'organisation des œuvres de l'assistance psychique à la jeunesse et aux enfants il se peut bien que certaines conclusions

doivent être tirées de cet étude. Ainsi il semble qu'il devienne impossible pour ce nombre restreint de psychiatres d'enfant, que nous possédons ou posséderons dans le proche avenir en Suède, d'examiner et de traiter tous ces troubles psychoneurotiques même les plus légers. La plupart de ces cas en ce qui concerne des écoliers doivent appartenir au médecin scolaire en collaboration avec les professeurs et aussi avec les psychologues scolaires. Quant à la division du travail entre les psychologues et les médecins il me semble que certaines missions doivent être traitées par eux d'une manière indépendante, bien entendu toujours avec la possibilité pour eux de s'entraider, si cela devient nécessaire. Quant aux troubles de conduite psycho-neurotiques il me semble bien évident qu'aucun cas ne doit être regardé comme définitivement diagnostique avant que le patient n'ait été soumis à une visite médicale quant aux troubles de conduite. Ici il s'agit, bien entendu, d'assortir, non pas d'être inférieur ou supérieur. Seul celui qui connaît la pathologie humaine peut faire un triage d'une façon satisfaisante.

Conclusions.

Le rapport est un rapprochement des cas de troubles de conduite nerveux chez des élèves dans la période commençante d'un district scolaire de Göteborg en les années scolaires 1945/46 et 1946/47 notés aux cartes de santé. Les renseignements à la base de ces notes sont pour 20 % des enfants livrés par les parents oralement aux examens médicaux à l'école, pour 13 % auparavant par un questionnaire sur l'état de santé de l'enfant et de la famille, prescrit dans les écoles primaires de Göteborg; à un pourcentage de 9 environ les institutrices ont rapporté ces troubles neurotiques et en 2 % des enfants ils sont diagnostiqués seulement à l'examen médical scolaire. Les troubles de cette matière de 879 élèves ne sont pas constatés par un autre examen ou interrogatoire que ceux habituels.

Non moins de 391 enfants = 44.5 % sont de cette façon trouvés présenter des troubles nerveux.

Les diverses formes de changement dans la conduite et aussi le pourcentage de ces formes sont indiquées par le tableau 2.

Les garçons sont selon le tableau 3 un peu plus nombreux entre les élèves neurotiques qu'entre les autres ($\text{diff } 6 \pm 3.4 \%$).

La pourcentage de l'enfant unique est 18.5 pour toute la matière; 20 % pour les enfant neurotiques et 17 % pour les autres, une différence d'une étonnante insignifiance. On ose peut-être présumer que les parents de cet enfant unique répugnent à porter un jugement qui puisse être compris comme une critique sur leur petit chéri (tableau 4).

Dans le chéma des examens médicaux de classe des écoles primaires à Göteborg il est noté si la constitution est typiquement trapue ou mince. Selon le tableau 5 les élèves sveltes sont les plus fréquents parmi les sujets neurotiques, et les élèves trapus les plus fréquents parmi les sujets de contrôle, dans tous les deux cas à un pourcentage de presque 7 (bel et bien 2 fois leurs erreurs moyennes).

«Le type neurolabile» est selon le tableau 6 chez les sujets neurotiques plus fréquent, c'est ici à un pourcentage de 39.4 comparé aux autres avec 27.3, une différence statistiquement significative ($12.1 \pm 3.14 \%$). Il est plus fréquent chez les garçons que chez les jeunes filles ($\text{diff. } 6.66 \pm 3.16$), plus fréquent parmi les enfants sveltes que parmi les enfants trapus ($\text{diff. } 7.67 \pm 4.5 \%$) plus fréquent chez l'enfant unique que chez les autres mais surtout le plus fréquent chez l'enfant isolé, c'est à dire l'enfant premier ou dernier d'un cercle de frères et sœurs, si l'intervalle d'âge entre cet enfant et les autres enfants de la famille est de plus de 3 ans ($\text{diff. vis-à-vis les autres } 8.89 \pm 3.8 \%$), ce qui semble indiquer que le type neurolabile est du moins à en certain degré un produit du milieu.

Le sujet neurotique offre un pourcentage insignifiant plus bas chez les enfants dans les familles où les pères de famille ont une profession de manchette que les autres (tableau 7).

Enfin les différents symptômes neurotiques sont analysés (tableau 8) et il est envisagé que les garçons dominent surtout quant aux difficultés de concentration, peur et angoisse, bégaiement, tics, mouvements nerveux, rongement des ongles, neuroses des organes. Le sucement du pouce domine d'autre part chez les

jeunes filles. Les trapus prédominent seulement d'ambition exagérée, inhibition et tension, tics, troubles du sommeil.

Presque 10 % des enfants uniques ont l'anorexie nerveuse. «l'enfant isolé» 8 %, comparé de 6.5 % chez les autres (la différence statistiquement incertaine: 3.26 ± 2.52 %).

L'enfant unique domine considérablement parmi les troubles de sommeil (l'absence des frères ou sœurs) comparé à l'enfant isolé (diff. $6.8 \pm 2,3$ %) et comparé à d'autres (diff. 5.1).

Comme conclusion administrative il est mis en lumière que les troubles psychoneurotiques même les plus légers sont trop nombreux pour être examinés et traités généralement par les rares psychiatres d'enfant de notre pays. La plupart de ces cas en ce qui concerne des écoliers doivent appartenir au médecin scolaire en collaboration avec les professeurs et aussi avec les psychologues scolaires.

Summary.

The investigation is based on a series of reports on nervous disturbances of behaviour recorded on the health registers of pupils of the elementary grades of one of the Gothenburg school districts for the school years 1945—46 and 1946—47. The average age of the children was 7 years. The information with reference to the nervous disturbances was in 20 per cent of the cases made by the parents' personally at the first medical school examination, in 13 per cent it was given in the form of answers in a questionnaire relevant to the child's state of health and familial conditions. Furthermore, the teachers have reported such nervous disturbances in 9 per cent of the children and in 2 per cent they were revealed at the routine school medical examination. The 879 pupils of the series have not been subjected to other examinations or questioning than that routinary in the Gothenburg elementary schools.

No less than 391 children, thus 44.5 per cent, have hereby been found to exhibit nervous disturbances.

The single child occurs to 18.5 per cent of the entire series, in 20 per cent of the neurosis cases and in 17 per cent of the remainder, a surprisingly small difference. Apparently certain

neurotic phenomena occur more commonly in the single child, while other disturbances again are more uncommon in these children. It may possibly also be assumed that the parents of the single child are more reluctant than others to report minor neurotic disturbances which may be interpreted as complaints against the child.

There is on the health cards of the Gothenburg elementary schools a column for specifications as to whether the bodily build may be considered as markedly slender or stocky. There is a greater incidence of the slender pupils in the neurotic material and of the stockily built in the controls.

The «neuro-labile type» is more common in the neurosis group and amounts to 39.4 per cent as against 27.3 per cent in the remainder. The type is more common among the boys than among the girls and more common in the single child than in the other groups, being most common in the «isolated child» (i. e. the first or last child of several siblings, if the interval between this child and the others exceeds 3 years), which seems to indicate that the neuro-labile type to some certain extent is a result of the environment.

In the neurosis group there is a somewhat lower incidence of children whose fathers are «white collar men», although the difference is not statistically significant.

Finally, the various nervous manifestation are analyzed in detail. It hereby appears that the boys are predominant with reference to difficulties of concentration, fear and anxiety, stuttering, tenseness, tics, motor restlessness, nailbiting and organo-neuroses. Finger-sucking is on the other hand most common in the girls.

Children with a pyknic build are predominant only in regard to exaggerated ambition, inhibitions and tenseness, tics and disorders of sleep, thus conditions that seem to be associated with psychic disturbances of relaxation and pace.

Nearly 10 per cent of the children have nervous anorexia, «the isolated child» in 8 per cent as compared with 6.5 per cent in the remainder.

The single child is more commonly represented with disorders

of sleep (absence of siblings) than the »isolated child» (that had siblings although with a large difference in age) and the remainder of the children.

The conclusion drawn from the investigation is that the milder forms of psychoneurotic disturbances of behaviour have to great an incidence to be examined and treated by the few child psychiatrists of our country. The majority of the uncomplicated cases in the school age should be managed by the school physician in co-operation with teachers and school psychologists.

Zusammenfassung.

Es wird über die in den Gesundheitstabellen eines Göteborger Schuldistriktes verzeichneten Fälle nervöser Störungen bei Schülern der Anfangsstufe in den Schuljahren 1945/46 und 1946/47 berichtet. Die Auskünfte, die diesen Tabellen zu Grunde liegen, wurden für 20 % der Kinder mündlich, für 13 % auf Fragebogen erteilt; bei 9 % wurden die nervösen Störungen von den Lehrerinnen gemeldet; bei 2 % der Kinder nur bei der schulärztlichen Untersuchung festgestellt. Das gesamte Material wurde nur den üblichen Untersuchungen u. Fragen unterzogen.

Bei nicht weniger als 391 Kindern von 879, d. h. bei 44,5 % wurden nervöse Störungen gefunden und zwar etwas mehr Fälle bei Knaben, als bei Mädchen.

Dass unter den »einzigsten» Kindern ein verhältnismässig geringer Prozentsatz (20 %) als neurotisch verzeichnet ist, dürfte vielleicht darauf beruhen, dass die Eltern dieser Kinder es vermeiden Auskünfte zu geben, welche für diese ungünstig sein könnten.

In Bezug auf die Körperbeschaffenheit zeigt sich, dass unter den neurotischen mehr »schlanke» als »untersetzte» Kinder sind.

Unter den Neurotikern herrscht der »neurolabile» Typ vor (39,4 %) und ist häufiger bei Knaben, als Mädchen, häufiger bei »schlanken», als »untersetzten», häufiger bei dem »einzigsten» Kind, als bei den andern, am häufigsten aber bei dem »isolierten» Kind, d. h. dem ersten oder letzten Kinde in einer Reihe von Geschwistern, wenn der Altersunterschied zwischen ihm und diesen mehr

als 3 Jahre beträgt. Dies scheint anzudeuten, dass der »neuro-labile« Typ wenigstens bis zu einem gewissen Grade ein Produkt des Milieus ist.

Das neurotische Kind kommt in Familien mit einem sog. »Manchetten-Beruf« des Vaters etwas seltener vor, als bei den anderen.

Von den verschiedenen neurotischen Symptomen überwiegen Konzentrationsschwierigkeiten, Furcht, Angstzustände, Stottern, Tiks, nervöse Bewegungen, Abnagen der Nägel, Neurosen verschiedener Organe, bei Knaben. Das Daumenlutschen ist bei den Mädchen häufiger. Die »untersetzten« Kinder sind nur in Bezug auf übertriebenen Ehrgeiz, Hemmung und Spannung, Zuckungen und Schlafstörungen in der Mehrzahl.

Fast 10 % der »einzigen« Kinder, 8 % der »isolierten«, Kinder (gegenüber 6,5 % bei den Übrigen) leiden an nervöser Anorexie. Ebenso herrscht das »einzige« Kind beträchtlich bei den Schlafstörungen vor (Fehlen der Geschwister) im Vergleich zu den »isolierten« und den anderen Kindern.

Die psychoneurotischen Störungen sind zu häufig, um auch in leichten Fällen von den wenigen Kinderpsychiatern unseres Landes untersucht und behandelt werden zu können. Die meisten Fälle, die Schulkinder betreffen, müssen dem Schularzt zugewiesen werden, der mit den Lehrern und Schulpsychologen zusammenarbeitet.

Resumen.

Se comparan casos de perturbaciones nerviosas en alumnos del periodo inicial de un distrito escolar de Gotemburgo, en los años escolares 1945/46 y 1946/47. Los datos anotados en las tarjetas han sido suministrados, en el 20 % de los niños, oralmente por los padres en los exámenes facultativos de la escuela; en el 13 %, por un cuestionario relativo a la salud del niño y de la familia; las institutrices han comunicado en un 9 % esas perturbaciones neuróticas y en un 2 % los niños han sido diagnosticados sólo por el examen médico escolar. Por lo tanto las perturbaciones de 879 alumnos no han sido constatadas por otro examen o interrogatorio que los rutinarios.

De esta manera se ha encontrado que nada menos que 391 (44.5 %) niños sufrían perturbaciones nerviosas.

El porcentaje de unigénitos es de 18.5 en total; el 20 % entre los alumnos neuróticos y el 17 % entre los otros, diferencia sorprendentemente insignificante. Se puede tal vez presumir que los padres de niños unigénitos se resisten a adelantar juicios críticos sobre sus hijos únicos.

En el esquema de los exámenes médicos en las escuelas primarias de Gotemburgo se ha anotado si la constitución del niño es típicamente fuerte o raquítica. Los alumnos esbeltos son más frecuentes entre los neuróticos y los raquíticos más frecuentes entre los sujetos a control.

El tipo neurolábil es más frecuente entre los neuróticos (39.4 %) que entre los otros (27.3 %). Es más frecuente entre los muchachos que entre las muchachas, entre los esbeltos que entre los raquíticos, entre los unigénitos que entre los otros y sobre todo más frecuente entre los hijos primogénitos o últimos si la diferencia de edad entre éstos y los otros hermanos es de más de 3 años, lo que parece indicar que el tipo neurolábil es, hasta cierto grado, un producto del ambiente.

El tanto por ciento de neuróticos es insignificamente más bajo entre los niños cuyos padres son oficinistas o dependientes que entre los otros.

Finalmente se analizan los diferentes síntomas neuróticos, observándose que predominan los muchachos sobre todo en lo que se refiere a dificultades de concentración, miedo y angustia, tartamudeo, tics, movimientos nerviosos, mordedura de uñas, neurosis de los órganos. El chuparse el pulgar es en cambio más frecuente entre las niñas. Los raquíticos predominan sólo en lo que se refiere a ambición exagerada, inhibición y tensión, tics, perturbaciones en el sueño.

La anorexia nerviosa se presenta entre los niños unigénitos casi en un 10 %, entre los niños «aislados» (primogénitos o últimos) en un 8 %, y sólo en un 6 % entre los otros. El unigénito predomina considerablemente en lo que se refiere a perturbaciones del sueño (ausencia de hermanos y hermanas) en comparación con el niño «aislado» y con los otros.

Como conclusión administrativa se ha demostrado que las perturbaciones psiconeuróticas, incluso las más leves, son demasiado numerosas para ser examinadas y tratadas por los pocos psiquiatras infantiles de nuestro país. La mayoría de esos casos, en lo que concierne a los escolares, deben dejarse en manos del médico escolar en colaboración con los profesores y los psicólogos escolares.

(FROM ULLEVÅL HOSPITAL, DEPARTEMENT I. PHYSICIAN-IN-CHIEF
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Nosocomial Chickenpox.

Some observations and attempts of prophylaxis.

By

PER ANCHERSEN.

The etiology and symptomatology of chickenpox are well known and the clinical diagnosis and the therapy of this disease are also generally dealt with uniformly in most of the textbooks and manuals.

The publications from the last years dealing with chickenpox have for a greater part discussed the relation of the disease to herpes zoster, as well as certain serious complications — especially encephalitis.

Generally chickenpox is such a benignant disease that it does not demand any great attention.

Nosocomial chickenpox however is very disturbing and one has as yet hardly any other means of getting rid of the disease in wards of younger patients, than to close the ward completely until the disease has been extinguished.

In Department I of Ullevål hospital we have had chickenpox in the course of 1945—46 in a couple of the wards of the department — especially in the scarlet fever ward. As the epidemic situation did not allow the complete shutting up of the ward it took several months for the chickenpox epidemic to die out. Altogether 93 cases of chickenpox occurred (6 women, 39 girls, 9 men, 39 boys). One had from this material the opportunity of studying certain sides of the epidemiology and symptomatology of chickenpox about which opinions still differ somewhat.

A closer description and discussion of this matter might therefore be of some interest.

The incubation period.

The incubation period is given with varying figures, as a rule between 2—3 weeks.

As there is as yet no full agreement as to *when* the chickenpox is contagious, the actual time of exposure to contamination is therefore in many cases difficult to define accurately. One cannot simply presume that a susceptible patient is infected the first day he is brought in to a ward where there are patients suffering from chickenpox, even if experience indicates that infection in most of the cases takes place then, especially if there are many patients in the ward with fresh outbreaks of the disease.

The first problem that appears is: When is chickenpox contagious?

F. ROLLY (1911) states that contamination is possible from before the rash appears and as long as there are scabs present. GORDON and MEADER (1929) found that the disease was only contagious in a very short period of time before the appearance of the rash, probably less than 24 hours. Also SHAMBERG (1945) emphasises the early infectivity.

With regard to the duration of infectivity, it is generally accepted that the chickenpox patients are not free from contagiousness before all the scabs are discarded.

THOMSON (1916) placed a patient suffering from chickenpox that had lasted 5—6 days in a ward with susceptible patients without it giving rise to any new outbreak of disease.

GORDON & MEADER (1929) admitted to a «pure» ward 4 patients with chickenpox 8, 11, 14, and 16 days respectively after the outbreak of the disease, without any occurrence of the disease taking place among the susceptible patients. They presumed that chickenpox is not contagious after the 10th day. JÖNSSON (1945) also states that chickenpox is only contagious in a short period around and just after the appearance of the rash.

In our epidemic secondary cases of chickenpox occurred 15 days after we had moved over to a «pure» ward one patient who, 16 days beforehand, had had an outbreak of chickenpox, and who still had scabs.

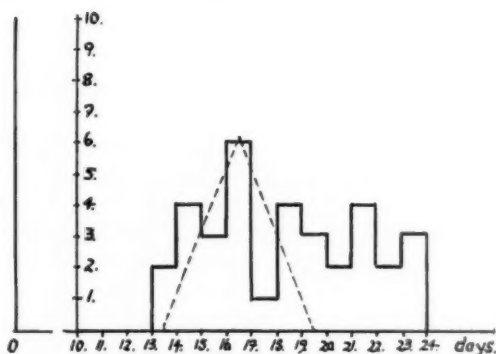


Fig. 1. Incubation period in 34 cases of chickenpox.

Fig. 1. shows the incubation period in some patients who were admitted to a scarlet fever ward where cases of chickenpox constantly occurred.

As far as the patients who were in the ward are concerned, their incubation period cannot be determined because the ward was not closed. One cannot therefore know with certainty whether they were exposed to infection from the primary cases or the secondary cases. Neither could the time of infection be recorded.

From the figure is evident that the major weight is grouped around the 17th day after the presumed exposure to infection, with a variation between the 14th and the 24th day.

We have presumed that the patients who were admitted to the chickenpox infected ward at the time when many of the children suffered from chickenpox in its various stages, were exposed to infection the same day they were admitted to the ward.

In these the incubation period was between 14 and 18 days. The patients who had the longer incubation period were those admitted to the ward when the chickenpox occurred more scattered and rarely. Therefore with regard to these patients it is not easy to determine the time when the infection took place, and this may explain why the incubation period appears to have been so long.

4 patients had an incubation period of 8 days. This refers to

a small group of patients who after having stayed 3 weeks in the ward, which at the time had been free from chickenpox for a long time, got chickenpox through a patient who had spent 6 days in the ward before his eruption broke out.

If the real incubation period is fixed to 14 days, it means that the primary patient was contagious already at the time of his admittance to the ward — 6 days before the appearance of his rash.

Such single observations of course can only be taken as suggestions at the most, but are however not completely valueless if they are supported by other observations.

Prodromal Symptoms.

There are usually no prodromal symptoms in chickenpox. BERGMANN (1941) puts little weight on the prodromes and states that there is a slight unwell-being and headache the last day and a half — or slight rise of temperature the last 2—3 days before the outbreak of the rash.

LICHTENSTEIN (1941), HARRIS and MITMANN (1946), SHAMBERG (1945) and TEISSIER (1922) state that the scarlet fever-like prodromal rash is not uncommon.

It is particularly studied and described by French clinicians. This *rash* may appear before, during, or after the outbreak of the actual chickenpox eruptions (P. J. TEISSIER), and is more often like scarlet fever but may resemble measles, or it may be polymorphic.

In 14 patients in our material there appeared an atypical rash that naturally can be divided into two main groups.

- A. Prodromal rash, distinctly separated from the chickenpox rash.
- B. Scarletiform rash which appeared approximately at the same time as the outbreak of the maculopapular-vesicular rash.

Group A. To this group the following 6 patients are calculated.

Case no. 1. (ref. no. 12941/46). Boy, 4 years old. Admitted for

scarlet fever on 24.6.46. Diagnosis verified. Transferred to chickenpox infected scarlet fever ward the following day.

10.7.46 — 15 days after admittance it is recorded in the hospital record: «Typical peeling off. Temperature uncertain. Approximately 38° C. the last couple of days. Today a pale red rash consisting of small papules, especially on the sides of the abdomen (relapse?). No angina.»

The following day the rash disappeared.

5 days later there came an outbreak of typical chickenpox, with the maximum temperature 38° C. Further development without complications.

Case no. 2. (ref. no. 17601/46). Boy 1½ years old. Admitted on 10.9.46 for scarlet fever. Transferred the following day to chickenpox infected ward. 26.9.46 — 15 days after transfer it is stated in the hospital record: «The last couple of days he has had a little fever with moderate degree of adenitis. Yesterday scattered maculopapules were seen on his abdomen which may resemble an outbreak of chickenpox. Today the rash is no longer present and the temperature is normal. On the 1.10.46 — 6 days after the fleeting eruption was observed, the patient got typical chickenpox.

Case no. 3 (ref. no. 18590/46). Boy, 4 years old. Admitted 24.9.46 with typical scarlet fever. Transferred the following day to the mentioned ward. The 8.10.46 — 13 days after the transfer it is stated in the hospital record: «The last week afebrile. Today slight rise in temperature to 37.5° C. The patient has the commencement of a chickenpox eruption with scattered red macules and papules. At the same time a large inflamed eruption is seen over the shoulders and nates.»

The day after the eruption was gone, and any remains from the presumed chickenpox efflorescence were not traceable despite meticulous examination.

The 15.9.46 — 7 days later the patient had an extensive outbreak of chickenpox with a temperature of over 40° C for 3—4 days.

Case no. 4 (ref. no. 18294/46). Boy 1½ years old. Admitted the 20.9.46 with typical scarlet fever. The day after transferred to the mentioned ward. After 5 days afebrile. The 4.10.46 — 13 days after transfer it is written: «The last couple of days he has been subfebrile. Today a number of red macules can be seen on the right arm and shoulder sharply outlined, about the size of a six-pence with raised centres to the shape of a point (vesicular formation?).»

The eruption disappeared the day after and the temperature sank again to normal. 16.10.46 — 12 days after the previous eruption and 25 days after the first possible exposure to chickenpox the patient got a typical chickenpox eruption with an uncomplicated development.

Case no. 5 (ref. no. 19503/46). Boy, 8 years old. Admitted the 6.10. 46 with typical scarlet fever. The day after transferred to the mentioned ward. 24.10. 46 — 15 days after the transfer it was written: »The last few days he has had a temperature of over 38° C. A large macular, partly confluent red eruption can be seen today on the back which is slightly irritant. Small red maculopapules with the commencement of vesicular formation can be seen spread about on the chest and back.» The described rash disappeared the day after, and the temperature sank to normal. 3 days later, the 27.10. 46, the patient got a new rise in temperature with typical chickenpox. The chickenpox elements were especially large and close together in that part of the back where the earlier red inflamed rash had been.

The further development was uncomplicated.

Case no. 6 (ref. no. 12640/46). Boy 2 years old. Admitted the 19.6. 46 with scarlet fever and scabies. The day after transferred to the chickenpox infected scarlet fever ward (there only occurred a couple of cases in this ward). After a lapse of 13 days he was moved back to a private room in the observation department because of room difficulties. 10 days later — the 13.7. 46 it is noted: »After 2 weeks with normal temperature the patient is today subfebrile. On the back and chest and the upper extremities one can see a pale red eruption and some bright red maculopapules the size of pinheads. (Chickenpox?). This rash completely disappeared the day after and the temperature fell to normal in the course of a couple of days. The 20.7. 46 the patient was moved to another scarlet fever ward where there was also chickenpox. 15 days later, the 4.12. 46 he got a general outbreak of a scarlet fever-like rash, mostly on the back. On the back, chest and the inside of the thighs considerable vesicles and pustules could be seen. The rash disappeared the day after, but the chickenpox eruption was typical with the temperature rising to 39.5° C.

The temperature sank to normal within 4 days. Uncomplicated further development.

Summary of the cases: In 6 scarlet fever patients who were exposed to contagion by chickenpox, fleeting red eruptions appeared approx. 2 weeks after the first possibility of infection, with greater or lesser pronounced maculopapular vesicular elements. The diagnosis chickenpox was made, but dismissed again when the rash did not last much more than a day.

In the first 5 patients typical chickenpox appeared 5—6—7—12 and 3 days respectively after the first eruption.

These 5 patients lay in the department where there continually

occurred new cases of chickenpox amongst the patients who lay in the department. With patient no. 6. there appeared a similar eruption 10 days after the last possibility for exposure for infection by chickenpox. (The moment for the first possibility of infection being 23 days beforehand).

15 days after the new exposure to chickenpox — 31 days after the previous exposure, the patient got typical chickenpox.

Discussion: JÖNSSON (1945) has on the basis of his investigations pointed out that a number of patients who are exposed to infection by chickenpox are not attacked by the disease the first time, but that they can get chickenpox by a renewed exposure to the infection a shorter or longer time afterwards. One does not know which factors in the contagious material, the method of infection or the infected person have any significance in this connection.

In every one of our 6 cases the earlier eruption described can naturally be explained as abortive chickenpox. The first 5 patients were fully exposed to the infection from the first day they were transferred over into the chickenpox infected department right on throughout the whole of the incubation period. The proper chickenpox eruption must therefore be taken to be due to infection at a slightly later moment.

On the basis of the first 5 cases one could imagine, as a pure hypothesis, that a reinfection at a later moment after the first infection, in some way interfered with it, so that it became weakened and only manifested itself in these abortive cases. A rough analogy with the bearing upon other virus diseases, e. g. poliomyelitis, where the infection by murine virus groups acts as a protection with monkeys who beforehand are infected with highly pathogenic monkey-poliomyelitis virus, influenza, encephalitis together with bacteriophages.

Case no. 6 seems however to indicate that an abortive chickenpox outbreak can also occur quite independant of such an infection, and in this manner represents a passage between the temporary immunity which is observed amongst others by Jöns-son, and the complete receptibility, which is surely the most frequent.

With our knowledge of the incubation period and the temporary contagiousness infectiousness in a number of chickenpox patients, there is nothing however to contradict the possibility that these 6 patients have been exposed for the infection at least twice, and that the fleeting eruptions described should rather be interpreted as abortive cases of chickenpox than as real prodromal eruptions.

Group B: Scarlatiniform rashes in connection with the outbreak of chickenpox (10 cases).

In 6 of these cases the diagnosis at admittance as well as the departments signing off diagnosis was: Chickenpox and scarlet fever.

With 3 of these patients there appeared scarlatiniform eruptions together with typical angina at the same time that the chickenpox broke out. In the 3 other cases the eruption appeared 3—5 days after the chickenpox rash. One of these patients had typical angina, whilst the other two had no throat symptoms.

One must assume that the infection by streptococci in these cases had taken place through the wounds formed by the broken vesicles, analogous with the method of infection with scarlet fever after burn wounds.

Unfortunately there were no cultivations taken from the erosions of the skin with two patients, so any actual proof for the correctness of the assumption cannot be supplied.

For the 4 other patients concerned the conditions were more confused and the diagnosis uncertain.

Case no. 13 (ref. no. 3750/45. 8 month year old girl). Admitted the 21.2.45 for scarlet fever? Chickenpox broke out 3 days beforehand. The day before admittance a general red rash. At the time of admittance: Temp. 39° C. Typical polymorphic chickenpox eruption. Moderate rubor in the fauces. No efflorescence of the mucous membranes. Eruption: On the body and extremities, and also suggestively in the face there was a dark red grouped and speckled arranged eruption, partly confluent, but without characteristic perifollicular arrangement. 2 negative samples from the throat and nose in view of hemolytic streptococci.

After two days residence, bilateral paracentesis was performed because of otitis on both sides. Growth of yellow hemolytic staphylococci from the pus in the ears.

After 20 days isolation she was transferred to the scarlet fever ward. There had not been any suspicious scarlet fever peeling. No secondary cases of chickenpox. The patient did not get scarlet fever during the stay.

The patient was signed off under the diagnosis: *Chickenpox (with erythema) complicated by Otitis media.*

Even if scarlet fever cannot be completely excluded, this diagnosis is however less probable. On the other hand it is not certain either that the eruption is connected with chickenpox.

Also with staphylococcal infections scarlet fever-like eruptions are seen. (ARANOW and WOOD 1942).

In no circumstance can the eruption be registered as a matter of course as prodromal chickenpox eruption.

Case no. 14 (ref. no. 3880/45) 3 year old girl. Admitted the 22.2.45. 4 days beforehand she had got chickenpox. The day before admittance: Temp. 37.6° C. Scarlet fever-like eruption with perifollicular formation and localisation as with scarlet fever. Angina with enanthema. Rhinosinusitis. White blood cells: 9 200 with 10 % eosinophilia. SR: 6 mm. Throat culture not taken.

After 20 days isolation transferred to the scarlet fever ward. No peeling had occurred. (With the exception that the chickenpox scabs were discarded). The patient did not receive scarlet fever during the further stay, and no secondary cases of chickenpox occurred.

It can hardly be said that there was any prodromal eruption, but it cannot be decided with any certainty if the eruption has had any connection with the chickenpox, or if there really was scarlet fever. The last named possibility seems to be the nearest.

Case no. 15 (ref. no 23312/46) 10 month old girl. Admitted the 14.1.46 for scarlet fever.

A couple of days before there had occurred a maculopapular eruption which was interpreted as chickenpox?

At the time of admittance the temperature was 37° C. There was a coherent strong erythema over the whole body, as well as the upper and lower extremities. Here and there a few vesicles could be seen.

The day after the temperature was 39° C. The erythema had disappeared but the chickenpox rash was in full bloom.

The patient was sent back to the childrens home where she had come from, where there had been chickenpox for some time.

A week later the child was admitted again in the department as a suspect for scarlet fever peeling.

The diagnosis was not confirmed in the department. Hemolytic

streptococci were not shown in the throat or nose, either during the 1st or 2nd stay in the department.

Case no. 16 (ref. no. 2313/46) 2 year old girl. Admitted the 14.1.46, together with the previous patient for chickenpox and scarlet fever.

The 12.1.46 she had got typical chickenpox with a temp. 39.8° C. The evening before admittance she had got a scarlet fever-like rash. At the time of admittance she had typical chickenpox with elements in all stages. In addition she had a scarlet fever-like eruption though without perifollicular arrangement. Fauces was pale. Temperature 40.8° C.

After penicillin treatment (7500 E \times 8) the temperature fell critically to normal the day after. The scarlet fever-like rash had disappeared the second day after admittance.

The 14.1.46 nothing could be seen, but the 15.1.46 considerable hemolytic streptococci in the throat, but not in the nose.

The case was not interpreted as scarlet fever in the department, and the patient was signed off after 6 days stay.

One week later she was again admitted into the department because she was peeling.

In the department they found an atypical peeling on the right hand side of the thorax.

In these last two cases scarlet fever diagnosis is very doubtful, and one is inclined to register these cases as a scarlatiniform rash in connection with chickenpox, without calling it a prodromal rash.

In many of the preceding cases one tried to get a closer diagnosis by carrying out Dicks and Schulte-Charltons reaction. But neither our toxin nor serum showed itself completely reliable, in that we saw negative Dicks reaction with several cases of quite certain scarlet fever. (With scarlet fever Dicks reaction is as known first negative in the course of a couple of weeks).

Similary in many cases we got urticarious serum reaction instead of bleaching by intracutaneous application of our streptococcus serum.

The epidemic situation in the case of those concerned from the childrens home did not give us any certain standpoint either, for there appeared scarlet fever as well as chickenpox there.

A summary of Group B. shows thus that in 10 of the chickenpox patients with a scarlet fever-like rash there were 6 certain scarlet fever cases. In 2 cases the eruption in all probability had

nothing to do with the chickenpox, whilst the scarlet fever-like rash as a result of chickenpox was fairly likely in 2.

One hardly makes any great mistake during a scarlet fever epidemic, by recording the scarlet fever-like rash accompanying chickenpox as scarlet fever, particularly when the scarlatiniform eruption occurs after the outbreak of chickenpox.

Phrophykaxis.

«The literature on chickenpox prophylaxis is extremely meagre» (GUNN 1932).

Even if nosocomial chickenpox is comparatively benignant, it carries with it nevertheless, considerable inconveniences both from the medical as well as from the administrative point of view.

Experiences in the last few years with regard to the importance of certain virus infections with congenital deformities makes it also natural to look upon chickenpox in a similar visual angle, even if this disease's importance in that respect is not proved.

OPPENHEIMER (1944) has further described a case of congenital chickenpox with wide-spread visceral manifestations, and for that reason one had already good grounds to take up the question of prophylaxis for investigation:

Active immunisation:

Attempt on active immunisation on similar lines as vaccination has been done by many, partly by inoculation (KLING 1913, HANDRICH 1914, ROBINOFF 1915, MICHAEL 1915, GREENTHAL 1926 and MEYER—STROMFELDT 1927) and partly by intravenous injection (HESS and UNGER 1918) of the vesicular content.

Most of the authors deal with comparable materials and have an optimistic attitude. But when one knows how capricious chickenpox can be in its contagiousness the publications do not strike one convincingly. SOLDIN (1923) HOFFMANN (1925) MITCHELL and RAVENELL (1925) together with WADDELE and ELEY (1927) correctly point out that an active immunisation can only take place if the individuals undergo chickenpox. And they find that the active immunisation both in principle and in reality is

of little value in overcoming chickenpox epidemics. The value of the intravenous immunisation is doubted in particular by THOMAS and MUNCH (1922).

Passive immunisation:

Encouraged by reports on the effectiveness of measles prophylaxis by injection of convalescence serum, BLACKFANE and COLL (1923) tried the same method in chickenpox.

GORDON and MEADER (1929) have given a survey of the experiences that were available until then, and as a whole they seem to give the impression that passive immunisation with convalescence serum really offered effective protection against chickenpox.

The convalescence serum was most effective when it was obtained in the first two months after the person had had chickenpox, and when it was given in doses of 10—15 ml.

GUNN (1932) gave 5 ml. serum as minimum doses, and after 3 years of age, he gave a number of ml. = the number of years \times 2.

Out of 43 immunised susceptible children, 10 got chickenpox (23.7 %). In the control material 50 % got chickenpox. In Gunns opinion this meant a protection of 26.7 % Really a very insignificant, not to say doubtful result when one considers the considerable amount of uncertainty attached to such an investigation.

Gunn recommended larger serum doses.

Without knowledge of the above mentioned experiments at that time, experiments were undertaken with passive immunisation against chickenpox in the summer of 1946 at Department 1, Ullevål Hospital.

Convalescence serum was produced after blood being taken from a patient three weeks after the outbreak of the disease. Doses: 5—10 ml. intramuscular. 10 persons (children at the age 1—6 years) were immunised directly before, or shortly after they were exposed to infection of chickenpox. 7 patients received chickenpox from 11—29 days after injection of serum. In all of them the incubation period was calculated from the first possibility of a natural infection to 17—24 days, with the reservation which had previously been taken with regard to the uncertainty

in determining the time of infection in cases with long incubation periods.

In one of the patients who received chickenpox 29 days after the injection of the serum the incubation period was unknown.

In three of the patients who did not get chickenpox, it was found by closer investigations that 2 of them had suffered from the disease previously. The third had not been exposed to chickenpox infection during the stay in the ward. As the experiments this gave quite negative results they were discontinued. The facilities have later not been suitable for further attempts with larger doses of serum.

JANEWAY (1944) tried gamma globulin in doses of 5—20 ml. without being able to notice any definite protecting effect against chickenpox.

Experiments with gamma globulin produced from convalescence serum do not appear to have been tried.

As shown by JÖNSSON (1945) the susceptibility for chickenpox is very varying and the possibilities of infection are difficult to judge with any greater degree of accuracy.

All of our serum-treated patients who later got chickenpox stayed for a longer period in a closed environment where fresh outbreaks of chickenpox constantly took place so that the possibility for infection must be presumed to be as great as possible.

This is perhaps the most simple explanation of the fact that our material is not in accordance with that of Gordon and Meader.

On account of the special epidemiological conditions there is strong ground to believe that chickenpox is an «airborne» infection. Attempts of sterilising the air by ultra-violet rays seems to indicate that this may be of importance in the reduction of the secondary cases in schools (WELLS and WILDER 1942) as well as in hospital wards (GREENE, BARENBERG and GREENBERG 1941, together with MEKHANN, STEEGER and LONG 1938).

Whether a further effectiveness of the prevention of «airborne» infection by means of oil impregnation and propylene glycol sterilisation plays any practical role in overcoming the nosocomial chickenpox only future investigations can decide.

Summary.

Some observations during a nosocomial chickenpox epidemic in Ullevål hospital, department I in 1945—46 are dealt with (93 cases).

The incubation period is found, in accordance with most other authors, to be 17 ± 3 days.

Some atypical eruptions are observed:

a) A polymorphous erythema of a little more than 24 hours duration occurred in 6 patients from $1\frac{1}{2}$ — $1\frac{1}{2}$ weeks before the proper chickenpox rash occurred. The epidemiological conditions seem to indicate that it was abortive cases of chickenpox. The possibility of interfering phenomena is mentioned.

b) Scarlatiniform eruptions in connection with the outbreak of the typical chickenpox occurred in 10 cases. In 6 cases it was chickenpox + scarlet fever. In 2 cases the eruption had most likely nothing to do with chickenpox, whilst in the last two cases it was most likely a scarlet fever-like rash in connection with chickenpox.

Attempts with prophylaxis by passive immunisation with convalescence serum in doses of 5—10 ml. did not succeed. 7 out of the 10 immunised patients received chickenpox. The remaining 3 cases avoided chickenpox for other reasons than immunisation.

The possibility of limiting or avoiding secondary cases of nosocomial chickenpox by overcoming the «airborne» infection according to modern principles is ventilated.

Résumé.

On rapporte quelques observations faites en 1945—1946 à l'Hôpital d'Ullevål, section I, lors d'une épidémie de varicelle nosocomiale (93 cas).

D'accord avec la plupart des autres auteurs on trouve que la période d'incubation comprend 17 ± 3 jours.

Quelques éruptions atypiques sont observées:

a) Chez 6 malades âgés de $1\frac{1}{2}$ — $1\frac{1}{2}$ semaine on a constaté un erythème multiforme durant un peu plus de 24 heures avant l'éruption propre de la varicelle. Les conditions épidémiologiques

paraissent indiquer qu'il s'agit de cas abortifs de varicelle. On mentionne la possibilité de phénomènes intervenants.

b) On a constaté dans 10 cas des éruptions scarlatiniformes en liaison avec l'éruption de la varicelle. Chez 6 cas il s'agissait de varicelle + fièvre scarlatine. Dans 2 cas l'éruption n'avait probablement aucun rapport avec la varicelle, tandis que dans les derniers 2 cas il s'agissait très probablement d'une éruption scarlatiniforme (Roseole) en combinaison avec la varicelle.

Des efforts de prophylaxis au moyen d'immunisation passive avec du sérum de convalescence en doses de 5—10 ml restaient sans résultat. 7 des 10 malades immunisés attrappaient la varicelle. Les 3 restants y échappaient pour des raisons autres que l'immunisation.

La possibilité de limiter ou d'éviter des cas secondaires de varicelle nosocomiale en surmontant l'infection par l'air, selon les principes modernes, est discutée.

Zusammenfassung.

Beobachtungen bei einer nosokomialen Windpocken-Epidemie (93 Fälle) im Krankenhaus Ullevål (1945—46). Festgestellte Inkubationszeit 17 ± 3 Tage. Einige atypische Krankheitsbilder:

a) Bei 6 ($1\frac{1}{2}$ — $1\frac{1}{2}$ Wochen alten) Kindern Auftreten eines ca 24 Stunden anhaltenden polymorphen Exanthems vor dem eigentlichen Windpockenausbruch. Es scheint sich um abortive Varizellenfälle, bzw. ein interkurrentes Phaenomen zu handeln.

b) In 10 Fällen ein scharlachartiger Ausschlag zugleich mit dem typischen Varicellaexanthem. 6 davon waren kombinierte Windpocken-Scharlach-Fälle, bei den anderen handelte es sich scheinbar um scarlatiniformes Exanthem (Rash) bei Varizellen.

Versuche einer Prophylaxe durch passive Immunisierung mit Rekonvaleszenten Serum in Dosen von 5—10 ml waren erfolglos.

Zur Begrenzung oder Verhütung sekundärer Varizellenfälle kommt Bekämpfung der »Luft« Infektion in Frage.

Resumen.

El artículo trata de algunas observaciones (93 casos) efectuadas durante una epidemia de varicela nosocomial en el hospital de Ullevål, departamento I, durante los años 1945—1946.

Se ha observado que el tiempo de incubación, de acuerdo con la mayoría de autores, es de 17 ± 3 días.

Se observaron algunas erupciones atípicas:

a) Una eritema polimorfa de una duración de un poco más de 24 horas se presentó en 6 enfermos de $1/2$ ó $1 1/2$ semanas antes de que el salpullido de la verdadera varicela apareciera. Las condiciones epidemiológicas parecen indicar que se trataba de casos abortivos de varicela. Se hace mención de la posibilidad de fenómenos de estorbo.

b) Erupciones escarlatiniformes en combinación con el brote de varicela típica se observaron en 10 casos. En 6 casos había varicela y escarlatina. En 2 casos la erupción no tenía seguramente nada que ver con la varicela, mientras que en los 2 últimos casos se trataba seguramente de un salpullido parecido a escarlatina en combinación con varicela.

Los ensayos con profilaxis mediante inmunización pasiva con suero de convalecencia en dosis de 5—10 milímetros no tuvieron éxito. 7 de los enfermos inmunizados contrajeron varicela. Los 3 casos restantes se libraron de la varicela por razones extrañas a la inmunización.

Se está discutiendo la posibilidad de limitar o evitar casos subsecuentes de varicela nosocomial venciendo a la infección por el aire, de acuerdo con principios modernos.

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The Duration of Immunity after Vaccination with BCG.

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It has been demonstrated, principally by Scandinavian workers (WALLGREN, HEIMBECK, SCHEEL, TÖRNELL, ANDERSON and BELFRAGE, NORDWALL, WINGE, HYGGE, etc.), that vaccination with BCG according to the principles initiated by Wallgren, gives definite protection against primary tuberculosis. It also, indirectly, gives protection against early post-primary forms of tuberculosis to a certain degree. In aiming, by means of this prophylactic immunization, at decreasing the morbidity and mortality rate — particularly in childhood and adolescence — the indications for BCG vaccination have, during recent years, been increasingly extended. In Sweden, for example, it is estimated that more than 200 000 such vaccinations are carried out each year, and in Norway, obligatory vaccination of tuberculin-negative persons has even been planned. Since vaccination with BCG has assumed such proportions, and includes persons who may possibly only be exposed to virulent tuberculous infection several years after vaccination, the importance of knowing *how long* the organism retains the artificial immunity brought about by BCG vaccination as against that due to virulent, exogenous tuberculous infection has become greater in practice. The basic principle for assuming that a tuberculin-negative individual can be considered as BCG vaccinated is that he is not exposed to tuberculous infection *before* the tuberculin reaction has become positive. It is, however, equally important that the person is tuberculin-positive after the vaccination even when virulent tuberculous infection occurs. Prophylactic tuberculosis measures should, thus, also be

directed at following the tuberculin sensitivity of the inoculated person and at performing revaccination when the BCG immunity has ceased.

As regards persons vaccinated with BCG, the duration of immunity is also dependent upon individual factors, and the exact duration of BCG immunity cannot, therefore, be fixed. By means of follow-up testing of a large series of persons vaccinated with BCG, it is, however, possible to obtain data concerning the approximate time at which it can be expected that the immunity in some cases will fail. The present investigation was carried out in order to contribute to this knowledge.

The question whether the terms «allergy» and «immunity» are theoretically to be considered as identical has been the subject of much discussion. As regards tuberculosis, BIRKHAUG and WIDSTRÖM have demonstrated that the terms are not synonymous. HEIMBECK, on the other hand, is of the opinion that they are synonymous. From a practical viewpoint, WALLGREN, TÖRNELL and others are rather of the opinion that tuberculin sensitivity is the best criterion for judging whether a person vaccinated with BCG is immune or not towards virulent tuberculous infection. This opinion was expressed by WALLGREN in 1927, and must even now be considered as predominating.

The first investigation dealing with the duration of immunity following vaccination with BCG was carried out by ANDERSON and BELFRAGE on material from Gothenburg. They made tuberculin tests on 905 persons vaccinated intradermally since 1927. Of these, 50 % were under 1 year and 75 % under five years of age at the time of vaccination. They found that 97.07 ± 0.1 % were positive for tuberculin up to 1.0 mg, and that none of those vaccinated between 1927 and 1931 — altogether 182 persons — were negative when tests were made in 1938. They divided the material into 3 categories:

- 1) 397 persons had lived in definitely tuberculous infectious surroundings,
- 2) 301 had not been exposed to tuberculosis,
- 3) for the remaining 207, the possibility of infection could not definitely be excluded.

The difference between the percentage of tuberculin-negatives in the above groups was not statistically established, and the authors were thus of the opinion that in these groups tuberculin sensitivity was not influenced by tuberculous superinfection.

As regards the importance of exposure, TÖRNELL, in his investigation published in 1947, reached a different result. He made a follow-up examination of 707 persons vaccinated with BCG between 1935 and 1940. 72 % were in the age groups up to 14 years at the time of vaccination. Törnell found a percentage difference of 13.9 ± 2.7 % between those exposed and those not exposed to infection. He is of the opinion that the results obtained by Anderson and Belfrage were dependent partly on the different methods of tuberculin testing — 87 % positive to the Hamburger test which, according to Törnell, would mean a certain number of pseudo-reactions, and also on the fact that the majority of the Gothenburg material consisted of infants. With a follow-up examination time of approximately 4 years, TÖRNELL found a negative or uncertain reaction (max. 10×10 mm) with 1.0 mg Mantoux in 18.5 ± 1.6 % for 568 persons not known to have been exposed to infection. With a similar follow-up time — 4 years — DAHL, HERTZBERG and REFSUM found, in material from Oslo, consisting of 2,354 persons (approximately 15 % school-children) only 3.6 % tuberculin-negative. In 1933, PARK, KERESZTURI and MISCHULOW made a follow-up examination on material from New York, and found a duration of allergy of two to three years. RYDÉN (1946) found in a follow-up examination of children vaccinated with BCG shortly after birth that after 1—2 years, 1.6 % of 122 children were tuberculin-negative, and 6.9 % of 249 children after 2—3 years. RINVIK (1944) found, in a small but well investigated series where exposure had been eliminated, that the immunity due to vaccination lasted only approximately one year. On the basis of a follow-up examination, BRINCHMANN (1935) recommends tuberculin testing and revaccination one year after immunization. WALLGREN (1945) is of the opinion that, even if BCG immunity can have a duration of 10 years, a considerably shorter duration must be estimated in individual cases, and he states that annual tuberculin testing is justified theoretically.

*all
variate*

Since this is not possible in practice, he suggests tuberculin control at the age of 3, 7, 15 and 21 years of age of all persons vaccinated with BCG. Since tuberculin tests are nowadays usually made in the schools, he suggests (1947) an additional testing at the age of 10.

The author's own material.

Since vaccination with BCG was earlier carried out in Stockholm chiefly on children, and since the youngest age-groups must be considered, from a point of view of exposure, as the most valuable, the material for the present investigation was selected from the records of children's hospitals in Stockholm. The Chiefs of the Paediatric Clinic at Norrtull's Hospital, Barnsjukhuset Samariteren, the Sachs Hospital for Children and of the City of Stockholm's Home for Children at Nyboda kindly allowed me access to the respective journals. In addition, the card-index of the Out-Patients' Department of Norrtull's Hospital was used. At the Home in Nyboda, healthy children are admitted on social grounds. On account of my limited time in Sweden, it was unfortunately impossible to include the clinic at Kronprinsessan Lovisa's Hospital for Children.

Tuberculin tests are made regularly on all patients in the wards of the above-mentioned hospitals. It was thus possible for me to obtain, from the journals, data regarding the tuberculin sensitivity and conditions of exposure of children who were earlier vaccinated with BCG. If there was any lack of clarity in the journals, inquiries were made at the patient's home, or information was obtained from the Central Dispensary of the City of Stockholm, whose chief physician kindly gave his permission. Moreover, through the Central Dispensary, 81 children vaccinated between 1938 and 1942, were summoned for a follow-up examination, although only 15 of them — due principally to inadequate postal address — replied to this call.

In this way, material was assembled comprising 1702 children, vaccinated intracutaneously, and tuberculin tested 6 months — 8 years after vaccination. The material is thus not selected, but entirely arbitrarily assembled. It must also be considered as

representative for Stockholm, despite the fact that exact figures for vaccinations with BCG carried out per year and age-group are not available. A comparison would probably show that an analogy exists between the present material and the total number of vaccinated children in the city.

Table 1.

Age-group when BCG vaccination was performed.

| 0—2 months | 3 months—2 years | 3—14 years | | |
|---------------|------------------|---------------|--------------|----------------|
| 833 49.0 % | 438 25.7 % | 431 25.3 % | | |
| | | 3—6 years | 7—9 years | 10—14 years |
| | | 289 17 % | 96 5.6 % | 46 2.7 % |

The table shows the age-groups, at the time they were vaccinated, of the 1 702 children submitted to a follow-up examination. It appears that nearly fifty per cent were vaccinated before the age of 3 months, and 75 per cent before the age of three years. This raises the value of the material from the point of view of exposure, since relatively dependable statements are available whether children in these age-groups have come into contact with infectious persons or not.

The result of the investigation.

In order to assess the duration of BCG immunity which, in practice, must be assumed to be equal to the duration of tuberculin sensitivity, the 1 702 children vaccinated and followed-up with tuberculin tests were divided into groups, according to the period which had elapsed between vaccination with BCG and tuberculin testing. In children who react positively for tuberculin, this can depend on three different factors:

- 1) Tuberculin sensitivity as a result of BCG vaccination
- 2) In addition, superinfection with virulent tubercle bacilli, whereupon the tuberculin sensitivity was further increased.

3) The tuberculin sensitivity has disappeared, and a virulent tuberculous infection has later brought about a spontaneous immunity.

It is thus natural that the tuberculin-negative group is more valuable as a criterion of the duration of the allergy, since artificial immunization has died out without virulent superinfection. This fact has also been emphasized by DAHL, HERTZBERG and REFSUM.

In order to assess a tuberculin reaction as extinct, the following criteria were set up: 1) tuberculin positivity at the latest 3 months after vaccination and 2) Mantoux test 1.0 mg at the moment of examination should, read after 72 hours, be less than 10×10 mm infiltration and redness.

Table 2.

Distribution in 1702 follow-up cases of children, BCG-vaccinated, in whom tuberculin sensitivity had disappeared.

| Time interval between BCG-vacc. and tuberculin test | 6 mths—1 year | 1 year | 2 years | 3 years | 4 years | 5 years | 6 years | 7 years | 8 years | Total |
|---|---------------------|---------------------|--------------------|---------------------|----------------------|----------------------|----------------------|---------------------|---------|----------------------|
| Total no. followed-up . . | 509 | 440 | 265 | 170 | 124 | 101 | 57 | 31 | 5 | 1702 |
| Negative for 1.0 mg Mantoux . | 21 | 33 | 24 | 16 | 14 | 15 | 10 | 3 | — | 124 |
| Negative, per cent | 4.12 $\pm 0.8\%$ | 7.50 $\pm 1.3\%$ | 9.0 $\pm 1.8\%$ | 9.35 $\pm 2.0\%$ | 11.29 $\pm 2.8\%$ | 14.85 $\pm 3.5\%$ | 17.54 $\pm 5.0\%$ | 9.67 $\pm 5.8\%$ | | 17.54 $\pm 0.1\%$ |

It was thus found, as seen from the table, that already 6—12 months after vaccination, 4.1 % become negative, 7.5 % after 1 year, 9 % after 2 years, 11.3 % after 4 years, and 17.5 % 6 years after vaccination. The fact that the figure for 7 years — $9.67 \pm 5.3\%$ — differs from this tendency must be ascribed to the low number in this group, altogether 34, as well, certainly, as the fact that the chances of exposure are greater than in the other groups.

A comparison with earlier investigations immediately shows that this is somewhat high, excepting the results obtained by TÖRNELL. The time interval of four years in his work is, however, an average time, in which are included observations on persons

vaccinated between 1935 and 1940. Moreover, the majority of his material consists of adults. If, in the present material, the cases which were subjected to exposure are subtracted, the percentage is somewhat higher than 11.3, on testing 4 years after vaccination.

Table 3.

Disappearance of tuberculin sensitivity in various investigations expressed in percentage of total number followed-up by examination 1, 2 and 4 years after vaccination respectively.

| Author | 1 year | 2 years | 4 years | Age at vaccination |
|----------------------------------|------------------------------|------------------------------|--------------------------------|---------------------------------------|
| ANDERSON & BELFRAGE | 251 : 8 $3.2 \pm 1.1 \%$ | 147 : 7 $4.7 \pm 1.7 \%$ | 93 : 2 $2.1 \pm 1.5 \%$ | 90% under 14 years 17% » 3 » |
| RYDÉN | 122 : 2 $1.6 \pm 1.1 \%$ | 249 : 17 $6.9 \pm 1.6 \%$ | — | Neonati |
| DAHL, HERTZBERG & REFSUM | 313 : 2 $0.6 \pm 0.4 \%$ | 218 : 7 $2.4 \pm 1.0 \%$ | 60 : 2 $3.2 \pm 2.3 \%$ | Adults, approx. 15% schoolchildren |
| TÖRNELL | — | — | 568 : 105 $18.5 \pm 1.6 \%$ | 72% under 14 years |
| WASZ-HÖCKERT | 440 : 33 $7.5 \pm 1.3 \%$ | 265 : 24 $9.0 \pm 2.8 \%$ | 124 : 14 $11.3 \pm 2.8 \%$ | 75% under 3 years |

We ask ourselves why the percentage varies considerably, even when allowance is made for the average error.

One explanation has already been mentioned, namely, the *individual factor*. The individual variation in sensitivity during the pre-allergic phase was already pointed out by WALLGREN in 1930. TÖRNELL (1947) showed conclusively, as regards later tuberculous conditions, that persons who show a strong tuberculous reaction and a strong local reaction after vaccination with BCG also retain their tuberculin sensitivity more strongly and for a longer period. After the pre-allergic phase, a reaction was obtained in 96.1% of individuals with a strong, and only 50% in those with a weak, local reaction and the tuberculin positivity remained in 95.2% in strong, and 69.4% in weak, local foci after 4 years.

TÖRNELL does not, however, state how these cases, which reacted strongly towards tuberculin, were distributed amongst

the different age-groups. It appears to me that the capacity of reacting strongly towards tuberculin is *dependent upon the age* to a very great extent, and that it is increased with increasing age, which appears later. In the investigations mentioned above, the age distribution varied considerably.

In intimate connexion with the age factor is a »hidden» — so to speak — exposure factor, whereas in the case of children of school age and later — despite no known source of tuberculous infection — it is never possible to avoid the suspicion that they were, nevertheless, superinfected.

There is still another possible factor, namely that the *BCG vaccine could have deteriorated* during the course of years. According to the control of the BCG strain in progress in Gothenburg, the Chief of the Bacteriological Laboratory there, Dr. ANDERS WASSEN, has stated (WALLGREN 1947) that the virulence has insignificantly decreased. The investigations of ANDERSON and BELFRAGE were based on vaccinations carried out between 1927 and 1937, those of DAHL, HERTZBERG and REFSUM principally between 1935 and 1940, those of TÖRNELL between 1935 and 1940 and that of RYDÉN between 1942 and 1946. The years during which vaccinations were carried out in Stockholm were between 1939 and 1946, and 85 % of them between 1943 and 1946, as seen from the Table.

Table 4.

Annual distribution of BCG vaccinations.

| 1939 and earlier | 1940 | 1941 | 1942 | 1943 | 1944 | 1945 | 1946 |
|------------------|-------|-------|-------|--------|--------|--------|--------|
| 0.9 % | 2.1 % | 3.4 % | 8.6 % | 13.1 % | 25.6 % | 33.0 % | 13.3 % |
| 85 % | | | | | | | |

This explanation appears acceptable, but it certainly only gives an incomplete reply to the question. *The exposure to virulent tuberculous infection* is certainly the deciding factor. ANDERSON and BELFRAGE found no difference in the tuberculin sensitivity under different conditions of exposure, whereas TÖRNELL in his material had 18.5 ± 1.6 % negative for those not exposed, and

4.6 \pm 2.1 % for those exposed to infection, as mentioned previously. In the Stockholm material, where only 6.4 % were known to have been in infectious surroundings, and 11 % had possibly been exposed to infection, it is found that *the difference in the tuberculin negativity in the various exposure groups is statistically established*, even if the certain and the uncertain cases were combined.

Table 5.

Tuberculin-positive and tuberculin-negative distributed according to conditions of exposure.

| | Definite exposure | Possible exposure | No known exposure |
|----------------------------------|-------------------|-------------------|-------------------------------|
| Tuberculin-positive 1566 | 106 | 183 | 1277 |
| Tuberculin-negative 136 | 2 | 5 | 129 |
| | 1.85 \pm 1.2 % | 2.66 \pm 1.1 % | 9.17 \pm 0.7 % ¹ |
| Total no. 1702 | 108 | 188 | 1406 |
| | (6.4 %) | (11.0 %) | (82.6 %) |

In addition to an individual factor — probably a varying power of immunization — superinfection and, in this case, probably a somewhat weakened BCG vaccine, the age at which BCG vaccination was performed also affects the BCG immunity. In order to demonstrate this in the Stockholm material, the material was divided into three groups, according to the age at which vaccination was performed, and the distribution of the tuberculin-negative cases within the different groups was also investigated.

It is thus evident that the children vaccinated as infants are tuberculin-negative 5 years or longer after vaccination in a greater percentage than in the group where the children were over 3 years at vaccination. The differences in these cases are statistically established. The cause is probably twofold. 1) The infant is considered as a poor former of antibodies and is clearly less capable of retaining immunity than older children. LIND's newly published work shows, however, that the reaction frequency after BCG vaccination is not so poor as was generally assumed. 2) As has

¹ The difference per cent between definite and no known exposure = 7.32 \pm 1.3 %.

Table 6.
Distribution of disappearance of tuberculin sensitivity according to the age of the child when BCG vaccination was performed.

| Time between vacc. and tuberculin-test | BCG-vacc. at 0—2 months | | | 3 months—2 years | | | 3 years—14 years | | | Time interval |
|--|-------------------------|-----------------------|-----------------------|------------------|-----------------------|-----------------------|------------------|-----------------------|-----------------------|---------------|
| | Fol. low-up exam. | Neg. for 1 mg Mantoux | Tuberculin-negative % | Fol. low-up | Neg. for 1 mg Mantoux | Tuberculin-negative % | Fol. low-up | Neg. for 1 mg Mantoux | Tuberculin-negative % | |
| 1/2—1 year . . . | 275 | 8 | 2.9 ± 1.0 % | 143 | 7 | 4.9 ± 1.8 % | 91 | 6 | 6.6 ± 2.6 % | 1/2—1 year |
| 1 year | 238 | 21 | 8.4 ± 1.8 % | 92 | 4 | 4.3 ± 2.1 % | 110 | 8 | 7.3 ± 2.5 % | 1 year |
| 2 years | 102 | 10 | 9.8 ± 2.9 % | 68 | 4 | 5.9 ± 2.9 % | 95 | 10 | 15.2 ± 3.7 % | 2 years |
| 3 years | 61 | 7 | 11.5 ± 4.1 % | 60 | 5 | 8.3 ± 3.6 % | 49 | 4 | 8.2 ± 3.9 % | 3 years |
| 4 years | 59 | 8 | 13.6 ± 4.4 % | 33 | 4 | 12.1 ± 5.7 % | 32 | 2 | 6.3 ± 4.3 % | 4 years |
| 5 years | 51 | 11 | 21.6 ± 5.7 % | 21 | 2 | 9.5 ± 6.4 % | 29 | 2 | 6.8 ± 4.7 % | 5 years |
| 6 years | 30 | 9 | 30.0 ± 8.4 % | 6 | — | — | 21 | 1 | 4.8 ± 4.6 % | 6 years |
| 7 years | 13 | 2 | 15.4 ± 10.0 % | 15 | 1 | 6.6 ± 6.4 % | 3 | — | — | 7 years |
| 8 years | 4 | — | — | — | — | — | 1 | — | — | 8 years |
| Total | 833 | 76 | 9.11 ± 0.99 % | 438 | 27 | 6.16 ± 1.15 % | 431 | 33 | 7.66 ± 1.28 % | Total |

already been briefly mentioned, the possibility of superinfection is intimately connected with the age factor. When it is a question of children of school age, the reliability of the information obtained from their parents, or by means of group examination, are limited as regards the chances of infection. This is particularly the case with children in a town or very large city.

It must be considered as unquestionable that the children who have been vaccinated with BCG in this Stockholm material, and who have obviously lived in tuberculous surroundings are not tuberculin-negative to the same extent as those who were not so exposed (Table 5). Amongst those who were tuberculin positive there must thus be a certain number of children who have been exposed to virulent infection. This circumstance results in the fact that *the percentages obtained for the tuberculin-negative children are somewhat on the low side.*

In order to determine whether tuberculin sensitivity amongst the tuberculin-positive cases was influenced by varying conditions of exposure, the material was divided into groups according to whether those examined reacted to the Hamburger test (Neo-tuberculin), Mantoux 0.1 mg or Mantoux 1.0 mg.

Table 7.

Tuberculin-positive grouped according to conditions of exposure and tuberculin sensitivity.

| Tuberculin test | Definite exposure | Possible exposure | No known exposure | Total | Difference % between definite and no known exposure |
|-----------------------------|------------------------|------------------------|-------------------------|---------------|---|
| HamburgerNeo-tuberculin . . | 90 84.9 \pm 3.5 % | 93 50.8 \pm 3.7 % | 538 42.1 \pm 1.4 % | 721 46 % | 42.8 \pm 3.6 % |
| Mantoux 0.1 mg | 11 10.4 \pm 3.0 % | 59 32.2 \pm 3.7 % | 357 28.0 \pm 1.3 % | 427 27.2 % | 17.6 \pm 3.3 % |
| Mantoux 1.0 mg | 5 4.7 \pm 2.1 % | 31 17.0 \pm 2.8 % | 382 29.9 \pm 1.3 % | 418 26.8 % | 25.2 \pm 2.5 % |
| | 106 | 183 | 1277 | 1566 | |

In ANDERSON and BELFRAGE's investigation, 87 % were positive for the Hamburger test and 5 % for the Mantoux 0.1 mg and no

statistically established difference between the exposed groups could be demonstrated. TÖRNELL obtained 21.3 ± 1.7 % Mantoux 0.1 mg for those not exposed, and 64.0 ± 4.6 Mantoux 0.1 mg or Pirquet positive for those exposed. The percentages I have obtained thus lie between the above-mentioned, and *the influence of the tuberculous superinfection appears unquestionable*, as in Törnell's investigation. Törnell's explanation of the different results obtained by him and by Anderson and Belfrage has already been mentioned. In my opinion, there is still another important factor, which applies in particular to the unexposed. Törnell's investigation was carried out four years after vaccination. That of Anderson and Belfrage, as well as my own, tuberculin tested later, are divided concurrently into several years with the greatest part of the material examined 1—3 years after vaccination. This explains the greater tuberculin sensitivity in our tuberculin-positive cases. By splitting up the material according to intervals of time between vaccination and tuberculin testing, it is namely possible to observe how the predominance of positive Hamburger reactions is distinct for the first years.

Since vaccination with BCG is very widespread in the Scandinavian countries and Finland, and since it chiefly comprises individuals from an environment free from tuberculous infection, it is necessary, on grounds already pointed out, *to carry out regular tuberculin tests on those vaccinated*. As was mentioned, Wallgren (1947) suggested that tuberculin testing and possible re-vaccination should be made *at least* at the following ages: 3, 7, 10, 15 and 20 years (child welfare centres, schools, conscription). These intervals, which are the most suitable from a practical viewpoint, also appear well-chosen in the light of the facts resulting from the present investigation, namely that *in Stockholm, 2—3 years after vaccination, 1 in 10 have become negative, and 2 in 10 after 5—6 years*. If tuberculin testing is omitted, there is a risk that those who are negative can suffer a virulent infection and contract tuberculosis, thus discrediting vaccination with BCG.

The question of the *efficacy of BCG* vaccination has been dealt with in a number of investigations (WALLGREN, HEIMBECK,

ANDERSON and BELFRAGE, NORDWALL, FERGUSON, TÖRNELL, etc.). The results of two investigations were published in 1946, and these illustrate in a most instructive manner the protection given by BCG vaccination, since adequate control groups are in existence.

HYGE described an epidemic of tuberculosis in a school in Denmark. Of those exposed, 105 were tuberculin-positive through an earlier virulent infection, 106 were positive after BCG vaccination and 94 were tuberculin-negative. In the first two groups, 2 children (1.9 %) as well as 41 (58.6 %) of the tuberculin-negative children contracted primary tuberculosis. The tendency to healing was best in the first group, and fairly good in the second, whereas in the third group, 1 died of tuberculosis and 6 later contracted phthisis.

ARONSON, in the U.S.A., stated that in 1936—1938, he vaccinated 1550 persons with BCG, whilst 1547 persons received an injection of physiological saline solution. The two groups were identical, and the ages between 0—19 years. Annual x-ray examination and tuberculin control were made. After 8 years, 4 of those who had received BCG vaccination and 28 of the control groups had died as a result of tuberculosis. The 4 deaths in the first group occurred 2 years after vaccination.

Papers whose apparent intention was to show the inefficacy of BCG vaccination have also been published. Thus, LEVINE and SACKETT (1946) stated that the mortality of tuberculosis amongst 1011 vaccinated children was 1.41 % and of 1073 unvaccinated controls from the same environmental and other conditions 1.51 %.

If we examine the case-histories in this paper, of those who contracted tuberculosis or died from it, it is found that the eight who died, and who had been vaccinated parenterally, were exposed to tuberculous infection *before* the vaccination took effect. According to accepted reasoning, these patients could not be considered as vaccinated, but should have been excluded from the group of «vaccinated». The possibilities of isolation, according to principle, are not possible in all cases, thus the cause of a higher morbidity of tuberculosis is not then due to a lack of protection

afforded by BCG vaccination, but to the insufficient application of the method. Such investigations only serve to show how a method can be discredited when its primary principles are disregarded.

In the Stockholm material, I find 6 children who, despite BCG vaccination contracted primary tuberculosis. It appears, however, that in 5 cases the tuberculosis was of particularly benign character owing to BCG vaccination. These 6 cases of primary tuberculosis comprise 5.5 % of the 108 BCG vaccinated, who were definitely exposed to infection. Two of the cases are reported by BIRKE (1946) and the remaining 4 cases are briefly reported here.

Case histories.

1. A girl, aged 4 years, who was BCG vaccinated shortly after birth, was isolated for 6 weeks and became tuberculin-positive. 3½ years later she had whooping cough, followed by measles 4 months afterwards. Tuberculin tests were not made. An old tuberculosis in the mother recurred simultaneously and the child was admitted to the children's department on social grounds. A suggested hilar reaction was found, and culture of the stomach lavage water gave a positive result. There was no registered period of fever. S. R. 15 mm/hr on admission. The tuberculous process had a mild course with fairly rapid roentgenological regression.

2. A girl, aged 8 years, who was BCG vaccinated at the age of 6. One year later she showed a negative patch test. Two years after vaccination, on routine x-ray examination at school, a parenchymal pulmonary infiltration, atelectasis and a mild hilar adenitis were found. The course of the disease, which took place without an initial period of fever, was estimated, after 2 months' hospital control, to have started 6 months earlier. X-ray control showed a stationary pulmonary condition, the patient had no fever whilst in hospital, and the S. R. showed normal values.

3. A boy, aged 4 years, BCG vaccinated at the age of 2, was isolated 6 weeks and then became tuberculin-positive. The father and a lodger had tuberculosis with tubercle bacilli in the sputum.

Was admitted to a children's hospital 2 years later for a very mild, pulmonary primary tuberculosis, free from complications.

4. A boy, aged 5 years, BCG vaccinated at the age of 2½. Positive to Mantoux 0.1 mg made 9 months later. Not controlled since then. The father, who had pulmonary tuberculosis, visited the home on leave from the sanatorium. He died of tuberculosis 6 months later. The boy suffered from initial fever and was admitted to a children's hospital, where x-ray examination showed bilateral hilar adenitis. The course of the disease was protracted. He was transferred to a children's sanatorium for convalescence.

Amongst the records which have been investigated, there were reports of further 2 children who had been BCG vaccinated and who died of tuberculous meningitis and miliary tuberculosis respectively. These cases were not, however, included in the 1702 followed up, since they were exposed to tuberculosis *before* they were tuberculin positive.

1. A 6 month-old refugee, born in a concentration camp. Arrived in Sweden on 28.4.45, at the age of 2 months, with compatriots of whom several were consumptives. Was then negative to 1.0 mg Mantoux and was BCG vaccinated in July. Became hyperpyretic in August with meningeal symptoms. Admitted to a children's hospital in Stockholm on 31.8.45, and miliary tuberculosis with tubercular meningitis was found. She died on 21.9. The diagnosis was verified at post-mortem.

2. A girl BCG vaccinated at the age of 13 days. Both parents tubercular. Contact with the mother ceased. Died 37 days later at the age of 1 month, 20 days of miliary tuberculosis. Autopsy revealed widespread tubercular lesions.

Three further cases belong to the series. Tuberculosis was suspected and they were admitted to Norrtull's hospital for 1—2 months for careful observation. No clinical, roentgenological or bacteriological foundation for the diagnosis of tuberculosis was found. Cold agglutination reaction was not performed (1945). Eosinophilia — 11 % — occurred in one of the cases, which led one to suspect a transient pulmonary infection.

In addition, 6 cases occurred, which were admitted into hospital with the diagnosis of primary tuberculosis. Clinical and roentgeno-

logical examination, however, revealed either bronchopneumonia or virus pneumonia. If such cases are not fully investigated it is possible that the belief in the efficacy of BCG vaccination may be undermined. It is, thus, impossible altogether to avoid the opinion that amongst the statements of tuberculosis despite BCG vaccination, there are occasionally cases of non-tuberculous nature.

Summary.

The investigation comprises 1702 BCG vaccinated children, who 6 months — 8 years later were tuberculin tested at children's hospitals in Stockholm. Half of those followed-up were, when vaccinated, under 3 months, and 3/4 under 3 years of age. A tuberculin reaction has been judged as negative when a Mantoux reaction 1.0 mg has not, after 72 hours, measured 10×10 mm. redness and infiltration.

After 2—3 years the tuberculin sensitivity disappeared in approximately 10 %, and after 5—6 years in approximately 20 % of those vaccinated. It is also possible to determine that a tuberculous superinfection considerably reacts on the tuberculin sensitivity. The difference in percentage between the approximately 6 % of the children who lived in an environment which was certainly infectious for tuberculosis, and the approximately 83 % who were not to our knowledge exposed to infection is $7.32 \% \pm 1.3 \%$.

Since BCG vaccination is nowadays largely performed also on children and young people from non-tuberculous surroundings, the tuberculin testing suggested by Wallgren at, at least, 3, 7, 10, 15 and 20 years of age is absolutely necessary, in order to ensure the effect of the BCG. A tuberculin test every, or every other, year gives, however, more complete certainty.

Of the 1702 children followed-up by examination, 6 developed primary tuberculosis. In 5 cases the disease had an extremely benign course. These 6 cases comprise 5.5 % of the 108 children who were definitely exposed to virulent tuberculous infection. No deaths occurred.

Résumé.

L'enquête comprend 1702 enfants BCG-vaccinés qui après 6 mois—8 ans furent testés de tuberculine dans des hôpitaux

d'enfants à Stockholm. La moitié de ceux observés avaient lors de la vaccination moins de 3 mois, tandis que 3/4 d'eux avaient moins de 3 ans. Une réaction de tuberculine a été jugée négative quand une réaction Mantoux de 1.0 mg n'a pas mesuré 10×10 mm de rougeur et d'infiltration après 72 heures.

La sensibilité à la tuberculine disparut après 2—3 ans chez 10 % env. et après 5—6 ans chez 20 % env. des enfants vaccinés. Il est aussi possible de déterminer qu'une super-infection tuberculeuse réagit considérablement sur la sensibilité à la tuberculine. La différence du pourcentage entre les 6 % env. des enfants qui vivaient dans des milieux indubitablement infectés de tuberculose et les 83 % env. des enfants qui, à notre savoir, n'étaient pas exposés à l'infection, est de $7.32 \% \pm 1.3 \%$.

Comme la vaccination par BCG est de nos jours exécutée en grande échelle aussi chez les enfants et les jeunes gens de milieux non-infectés de tuberculose, le test de tuberculine à l'âge d'au moins 3, 7, 10, 15 et 20 ans, proposé par Wallgren, est absolument nécessaire pour assurer l'effet du BCG. Cependant, un test de tuberculine fait chaque année ou tous les deux ans donne une sûreté plus complète.

Des 1702 enfants observés par des examens, 6 développaient une tuberculose primaire. Dans 5 cas la maladie avait un cours extrêmement bénin. Ces 6 cas comprennent 5.5 % des 108 enfants qui étaient définitivement exposés à une infection virulente tuberculeuse. Aucun cas de mort.

Zusammenfassung.

1702 BCG-geimpfte Kinder wurden 6 Monate—8 Jahre später einer Tuberkulinprobe unterzogen. 50 % waren bei der Impfung weniger als 3 Monate, 75 % weniger als 3 Jahre alt. Die Tuberkulin-Reaktion wurde als negativ bezeichnet, wenn eine Mantoux-Reaktion 1.0 mg nicht nach 72 Stunden eine Rötung und Schwellung von 10×10 mm ergab.

Nach 2—3 Jahren verschwand die Tuberkulinempfindlichkeit in ca 10 %, nach 5—6 Jahren bei ca 20 % der Geimpften. Eine Tuberkulose-Superinfektion wirkt erheblich auf die Tuberkulinempfindlichkeit ein. Der Unterschied zwischen den ca 6 % der

Kinder, die in einer sicher Tbc-ansteckenden Umgebung wohnten und den ca 83 %, die keiner Infektion ausgesetzt waren, beträgt $7,32 \% \pm 1,3 \%$.

Da heutzutage die BCG-Impfung vielfach auch bei Kindern und Jugendlichen aus tuberkulosefreier Umgebung vorgenommen wird, ist die von Wallgren vorgeschlagene Tuberkulinprobe im Alter von 3, 7, 10, 15 und 20 Jahren unbedingt nötig, eine Probe jedes oder jedes zweite Jahr gibt vollständige Gewissheit.

Von den 1702 beobachteten Kindern entwickelten 6 ($=5,5 \%$ der 108 einer sicheren Infektion ausgesetzten Kinder) eine primäre Tuberkulose, die in 5 Fällen äusserst mild verlief. Todesfälle traten nicht ein.

Resumen.

El artículo se refiere a 1702 niños vacunados con BCG. 6 u 8 meses después, en el Hospital Infantil de Estocolmo, fueron objeto de pruebas con tuberculina. La mitad de los niños tenían, al ser vacunados, menos de 3 meses. Menos de 3 años tenía el 75 % de los niños. La reacción tuberculínica ha sido considerada como negativa en los casos en que la reacción «Mantoux» 1,0 mg, después de 72 horas, medida 10×10 mm, no presenta rojez ni infiltración.

Después de dos o tres años la sensibilidad tuberculínica había desaparecido en el 10 % y después de 5 ó 6 años en el 20 %, aproximadamente, de los vacunados. Así pues la superinfección tuberculosa reacciona sobre la sensibilidad tuberculínica. La diferencia entre el 6 % de los niños que vivían en un medio ambiente infeccioso para la tuberculosis y el 83 % que no se hallaban expuestos a infección, es: $7,32 \% \pm 1,3 \%$.

En vista de que la vacuna BCG se usa hoy día también para niños y jóvenes que proceden de un medio ambiente no tuberculoso, es absolutamente necesaria, para garantizar el efecto de BCG, la prueba tuberculínica propuesta por Wallgren a los 3, 7, 10, 15 y 20 años, como mínimo. Sin embargo, da una seguridad más completa el que la prueba se realice cada año o cada dos.

De los 1702 niños examinados, 6 desarrollaron tuberculosis primaria. En 5 de dichos casos la enfermedad siguió un curso

sumamente benigno. Estos 6 casos representan el 5,5 % de los 108 niños que fueron definitivamente expuestos a una infección de tuberculosis virulenta. No hubo ningún caso de muerte.

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Rheumatic Pneumonia.

By

E. VAN WIJK.

Two children were admitted within a short time to the Pediatric Clinic and at about the same time a third patient was seen in the Wilhelmina-Gasthuis at Amsterdam, all three having complaints of rheumatic nature, associated with pulmonary disturbances.

I. In the winter of 1944—1945 the first patient, a girl of 5 years, had suffered from swelling and pains in the joint regions for four weeks.

Four weeks before admission to the hospital (Dec. 28, 1946) she had had an exanthematous illness, accompanied by fever and sore throat, and considered by her mother to be Rubella. Three other children in the family had had the same illness, but none of them had shown peeling of the skin. The patient had not been well since then. Two weeks before admission she again had pains in the joints, «flitting» from knees and feet to her shoulders and fingers. She complained of pain over her heart, and had been short of breath for about a week. On admission the girl was very ill and dyspnoeic, with a pale cyanotic skin, and she showed superficial, rapid respiration, with slight indrawing of the flanks. The throat was red. There was enlargement of the heart to the right and also to the left as far as the anterior axillary line. On auscultation a rough systolic murmur was heard, with a ringing first sound and a loud second sound in the pulmonary area.

On the left side posteriorly, near apex and base of the lung, there was impairment in the percussion note and many high-pitched and moist rhonchi were heard. The liver was palpable two finger-breadths below the costal margin, but the spleen was impalpable, and there were neither edema nor skin nodules. The

patient's fingers showed clubbing, while the thumbs were held in a position of slight flexion. None of the joints was swollen or warm to the touch. The child complained of pain over the heart, in the left shoulder and in the right thumb.

The bloodpicture was as follows: haemoglobin: 75 %, red blood cells 4 000 000/cmm, white blood cells 11 000/cmm. Differential white cell count: »Stab»polymorphus 15 %, segmented polymorphonuclears 59 %, lymphocytes 22 %, monocytes 3 %, eosinophils 1 %. Blood sedimentation rate 125 mm in 1 hour. We immediately commenced treatment with sodium salicylate and sulphadiazine. When it was found that the salicylate preparation caused vomiting a change was made to pyramidon. The lung changes increased in severity. On the left side, above the heart, and on the following day on the right side as well, a pleural friction rub was heard. The dullness on percussion became more widespread and bronchial breath sounds were heard between the dull area and the apex. The patient became steadily more dyspnoeic and died on Jan. 1 1947.

II. On Dec. 19, 1946 the second patient, a little girl aged 14 years, was admitted to the Wilhelmina Gasthuis (department under temporary charge of Dr. GODFRIED).

She had started a fever on Dec. 6, and began to cough on Dec. 7, while a few days before admission she had some pain in the left fore-arm. On admission she was seriously ill, cyanotic and somewhat dyspnoeic, and had a slightly clouded consciousness. Herpes labialis was present; the tonsils were mildly enlarged. Auscultation of the heart, enlarged to left and right, showed a systolic murmur and also gallop rhythm. On the right side posteriorly the breath sounds were faint with a few rhonchi, and more superiorly some bronchial breathing was heard. Anteriorly, on the right side close to the heart, a dull note was found on percussion, with a friction rub audible over this area.

On the left side posteriorly, towards the base of the lung, there was a small zone of total dullness on percussion, continuing superiorly into an area, percussion of which produced a moderately impaired note. In the middle zone of the left lung posteriorly there was distinct bronchial breathing. Percussion of Traube's

space produced a dull note. The liver and spleen were just palpable.

The left wrist joint had a higher temperature than the right, and was red and swollen, with some limitation of movements. The patient's temperature was slightly raised; the blood pressure was 120/70 mm Hg.

Bloodpicture: haemoglobin 60 %, red blood corpuscles 3 400 000/cmm, leucocytes 12 100/cmm. Differential count: »Stab«cells 6 %, segmented polymorphonuclears 66 %, lymphocytes 23 %, monocytes 4 %, metamyelocytes 1 %. Blood sedimentation rate 134 mm/hour.

Blood culture: sterile. Wassermann reaction: negative.

A start was made with the administration of aspirin and penicillin. When it appeared that neither the temperature nor the general condition had improved in 6 days, penicillin therapy was ceased. During this period the wrist manifestations disappeared on the left side, though the right side became involved, and at the same time erythema nodosum appeared on the extremities. The changes in the left lung improved slightly and the apex beat was felt close to the position expected from light percussion of the heart; so it was decided that myocarditis was present, rather than pericarditis, especially as the dullness over the right lung posteriorly became less marked.

The general condition deteriorated rapidly, and the girl became more and more dyspnoeic, dying on Dec. 30 in a state of shock.

III. The third case was a boy of $7\frac{1}{2}$ years, who had had a cough for 2 months, and fever and signs of pulmonary disease for 1 month, not responding to the administration of sulphathiazol. After a chest X-ray had been made by the consulting specialist, pleural puncture was tried, but no fluid was obtained. The boy was admitted after this, on Nov. 18, 1946. He was obviously ill and somewhat dyspnoeic, with a temperature of 39° C. The throat was inflamed; the left half of the thorax did not move well on respiration; there was no enlargement of the heart, and the heart sounds were closed in all areas. In the midzone of the left lung posteriorly, and in the flank, the percussion note was impaired, and there was faint bronchial breathing with a few sibilant rhonchi

below the angle of the scapula. Slight enlargement of the liver was present, but the spleen was not palpable.

The blood picture was: haemoglobin 70 %, red blood cells 4 100 000/cmm, white blood cells 16 000/cmm. Differential white blood cell count: «Stab»cells 2 %, segmented polymorphonuclears 70 %, lymphocytes 27 %, monocytes 1 %. No toxic granulation. Blood sedimentation rate 120 mm/hour.

An X-ray of the chest, made on the day of admission, showed infiltration of the left lower lobe. Since the child had had adequate doses of sulphathiazoltablets at home, without effect, we considered this at first to be a virus pneumonia. Cold agglutination titre was positive at 1/64, but after a few days it decreased to 1/8, (a titre of 1/128 being considered as a definite positive result). We waited until the day after admission before commencing penicillin therapy. The temperature fell as a result and remained normal for a week. The general condition showed no change and no noticeable alteration occurred in the findings on auscultation of the lungs.

Ten days after admission the temperature rose again; a few days later the child began to complain of pains in the knees and in the sole of the right foot. The joints were not swollen, and although painful, could be moved fairly well. No nodules were present, neither erythema annulare. The pulmonary findings remained unchanged. Treatment was then begun with 3 gram sodium salicylate per day for 1 week, as a result of which the joint manifestations became slightly less. The temperature, however, remained raised, and as the child complained of nausea, penicillin therapy was recommenced, with some reduction of the fever. There was a further rise in temperature after this. The patient was then given pyramidon, the pains in the joints disappearing completely in a few days. The temperature was normal after Dec. 27. About this same time there was some improvement in the pulmonary infiltration, the progress of which had been followed radiologically. There was a decrease in the blood sedimentation rate during the following months, to 5 mm in one hour, and the child felt very well. The blood picture was satisfactory, and four months after admission the patient was discharged. Al-

though the pulmonary infiltration appeared, on X-ray examination of the chest, to have resolved entirely, there persisted a slight impairment of the percussion note.

A brief summary follows of the autopsy-findings in the two cases which died.

In the first (autopsy performed by Dr. R. VAN DAM) a large number of warty vegetations were found in the heart valves. The upper lobes of the lungs were very firm in consistence, and at microscopic examination many endothelial cells inside the alveoli were seen. The walls of a few alveoli showed very clearly the presence of «couennes».

In the second case (autopsied in the laboratory of Prof. DEELMAN) inflammation of the heart valves was also seen, while the lungs showed thickened alveolar walls, with «couennes» and «bourgeons» (see below).

Comment:—As is well known, many investigators are of the opinion that in rheumatism there is no question of the direct effect of the infecting agent, but rather an individual, variable sensitivity to bacterial and other antigens, in which instance a focal infection could stimulate a state of hypersensitivity. Foreign antigens are able to lead to the production of antibodies, which, when they come in contact with vascular tissue with previously sensitised endothelium, can cause definite reactions. Such reactions become manifest as the lesions which we see in rheumatic pneumonia, and which resemble the lesions of a glomerulonephritis developing after scarlet fever. The manifestations of the lesions in the lungs are: increased permeability of the capillaries, with transudation and leucocyte infiltration of alveoli, septa and interlobular areas. Swelling of the inter-alveolar septal cells, with pyknotic changes in the nuclei, is sometimes observed as part of anaphylactic reactions. As a result the separating walls of the alveoli break down, and intra-alveolar haemorrhages occur. The transudate is compressed against the walls, and undergoes organisation. Membranes are thus formed, the so-called «couennes». The plugs which fill the alveoli are fixed, by means of processes of their substance, to the cells of the septa, and are termed «bour-

geons» after organisation has taken place. It is not surprising that we did not find this in our first patient, as this case died so soon after the onset of the condition that there was no time for the development of the organisation.

GRIFFITH et alia investigated a group of 1046 patients with rheumatism, amongst whom pneumonia was found in 119, i. e. 11.3 %. They distinguished three types of pneumonia:

- 1) Primary acute rheumatic pneumonia;
- 2) Secondary acute rheumatic pneumonia;
- 3) Subclinical pneumonia.

The primary acute rheumatic pneumonia is the first symptom of the disease. The patient is ill, with fever, cough and dyspnoea, along with marked dullness on percussion of the lungs, and rhonchi and bronchial breath sounds. After a few days symptoms and signs of polyarthrititis and sometimes also of carditis develop. Neither pathogenic bacteria nor leucocytes are to be found in the sputum. There is a moderate leucocytosis, and a raised blood sedimentation rate. The illness generally lasts for some time; there may be widespread extension of the lungchanges, leading sometimes to a serious want of oxygen.

The secondary acute rheumatic pneumonia develops at the same time as the polyarthrititis, especially in cases with the polycyclic type of rheumatism. Dyspnoea is present, the patient has a cough, and is mentally restless. There are dullness on percussion and fine rhonchi on auscultation of the lungs.

There are no true symptoms of the subclinical pneumonia, although the patient is more ill than could be expected from the clinical findings. An X-ray of the chest shows a mottled appearance in the region of the hili and in other areas of the lung fields.

GRIFFITH et alia have stated that the X-ray findings are of special interest on account of the rapid onset and resolution of the infiltration, which occasionally appears to «flit» from place to place. There is generally no displacement of the mediastinum, although often an exudative pleuritis is present, which may disappear quite rapidly.

Differential diagnosis is not easy, and this disease cannot be distinguished from an atypical pneumonia by clinical or radio-

logical investigation, or by sputum or blood examination. Rheumatic pneumonia may only be diagnosed with certainty when there are accompanying signs and symptoms, characteristic of rheumatism such as polyarthrititis, carditis, purpura or erythema annulare. Bacterial pneumonia has a sudden onset with a rigor, high temperature and characteristic sputum; the causative organisms may be cultured from the sputum. Tuberculous pneumonia can be distinguished by the history of contact and the course of the inflammatory process. One must be careful in diagnosing between rheumatic pneumonia and a right-sided cardiac failure, in which air-hunger and high venous pressure are prominent, the liver is soft and enlarged, and an early development of oedema is present. As a rheumatic pneumonia often precedes these cardiac symptoms one must not forget the possibility of a concurrence of the two conditions. The anti-streptolysin-titre is raised only in cases of rheumatism, whether with or without pulmonary disturbances, and may be of much use when considering the differential diagnosis.

On further consideration of these cases it is seen that two of the children had rheumatic manifestations and pneumonia simultaneously (in one case there existed the possibility of a recurrence of the rheumatic fever), while in the third case the rheumatic symptoms developed after the illness had commenced with pulmonary inflammation which did not respond to chemotherapy. Since we could not decide immediately whether this was croupous pneumonia or not, we began treatment on nonspecific lines; in the first case we gave aspirin and sulphadiazine, while the second girl and the boy were treated with aspirin combined with penicillin. In retrospect, it would have been wiser to have given the first girl penicillin as well, instead of sulphadiazine, for the administration of sulphadiazine to cases of acute rheumatism may be accompanied by more severe toxic reactions than when it is given in other diseases. As none of the pulmonary changes responded to the treatment which we are accustomed to use in cases of croupous pneumonia, we must consider the diagnosis in the first two cases to have been secondary acute rheumatic pneumonia, while in the third case it was primary acute rheumatic pneumonia. It is well

known, that recurrences of rheumatic fever often occur, and that there is considerable risk that the heart, not involved in the first attack, may then suffer damage. In many instances of acute rheumatism there is a subsequent, more or less permanent invalidism, while a large number of young people die, having suffered from carditis for a long time. The cases of rheumatic fever associated with rheumatic intrapulmonary processes form a new group, exposed to even greater danger.

It becomes more and more obvious that the initiative shown by COBURN in attempting to prevent the recurrences of rheumatic fever by the administration of small amounts of sulphadiazine, is beginning to bear fruit. On account of this we treated the last mentioned patient according to the directions suggested by COBURN. One single publication has appeared to date, discussing the possibility of the use of penicillin as a prophylactic measure against the recurrence of rheumatic attacks. Further investigation along these lines still is necessary.

Summary.

Three little patients are described with acute rheumatism and pulmonary abnormalities. With reference to literature the author discusses the reasons for the diagnosis of rheumatic pneumonia and the therapy in such cases.

Résumé.

On décrit trois petits patients atteints de rhumatisme aigu et d'anomalies pulmonaires. En se référant à la littérature l'auteur discute les raisons du diagnostic de pneumonie rhumatismale et de la thérapeutique dans tels cas.

Zusammenfassung.

Es werden drei Fälle von Rheumatismus mit Lungenveränderungen beschrieben und die Begründung der Diagnose »rheumatische Lungenentzündung«, sowie die Therapie solcher Fälle besprochen.

Resumen.

Se estudian los casos de tres niños enfermos que padecen de reumatismo agudo y anormalidades pulmonares. Refiriéndose a la literatura médica, el autor discute diversas opiniones y motiva la diagnosis de neumonía reumática y la terapia para tales casos.

Note at the correction.—Since this report was completed an article was published by E. E. MUIRHEAD and A. E. HALEY, describing a case of a woman who died from acute rheumatic fever and rheumatic pneumonitis. The authors also gave an interesting review of the most important observations on this condition and discussed the various theories on the nature of the pulmonary lesions. (E. E. MUIRHEAD and A. E. HALEY, Arch. Int. Med. 80, 328, 1947.)

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Studies on Diphtheria.

I. The decrease of natural antitoxic immunity against diphtheria.

By

BO VAHLQUIST.

During the years preceeding World War II the frequency of diphtheria was very low in many countries of Europe. Among the exceptions were England and Germany. In England the morbidity rate in diphtheria was rather high but decreasing, in Germany it was not only high but also steadily increasing.

During the war there was over the entire continent a general increase in frequency and graveness of the malady. In many countries the diphtheria problem outweighed in importance by far that of all other acute contagious diseases. The data given in table 1 throw light upon this situation.

The evolution in Sweden is followed more in detail in the following figure 1.

Provided that there is a periodicity of some twenty years in regard to the recurrence of the big epidemics of diphtheria (Ohlin, 1936) such an epidemic might, in fact, have been expected in the late thirties. It can hardly be doubted, however, that in this case the outbreak of World War II was of great, even decisive, importance. The heavily infected German troupes, often carrying diphtheria of the type *gravis*, have probably played a fatal rôle in transmitting the disease to the populations of occupied countries. To Sweden the stream of refugees carried the infection from Finland and the Baltic. A great number of the cases of diphtheria, and still more diphtheria carriers, registered in Sweden during the war were, indeed, among the refugees themselves or could be directly traced to contact with such cases among aliens. The close

Table 1.

Diphtheria frequency in different countries of Europe. The values represent annual number of cases of clinical diphtheria in 100.000 inhabitants.

| COUNTRY | 1930 | 1935 | 1938 | 1943 | 1945 |
|-------------|------|------|------|------|------------|
| SWEDEN | 69 | 14 | 2 | 38 | 33 |
| DENMARK | 152 | 103 | 23 | 64 | 70 |
| SWITZERLAND | 111 | 44 | 9 | 85 | — |
| FRANCE | 56 | 41 | 40 | 111 | — |
| NORWAY | 50 | 21 | 7 | 760 | 250 |
| FINLAND | 28 | 109 | 81 | 370 | 488 |
| NETHERLANDS | 93 | 21 | 15 | 630 | 800 |
| HUNGARY | — | 102 | 69 | 55 | INCREASING |
| ENGLAND | 186 | 160 | 159 | 85 | 60 |
| USSR | 91* | 60* | 56* | — | — |
| GERMANY | 109 | 200 | 223 | 341 | — |

The data in this table are collected from the «Statistiques des maladies à déclaration obligatoire» of the «Organisation d'hygiène» of the United Nations for the time 1930—38 and from the UNRRA Epidemiological Information Bulletin for the time 1943—45. The numbers with an asterisk are approximate.

time relation between the increase of the number of foreigners in Sweden and the increase of the diphtheria cases is obvious from the following diagram (fig. 2).

It is quite natural that the medical authorities of Sweden feared the outbreak of a new severe epidemic of diphtheria when the annual number of cases rapidly augmented in the early forties. But the wave subsided before assuming fatal proportions. Scrupulous quarantine of the refugees as well as large scale immunization of the Swedish children have undoubtedly contributed to this favourable outcome. Nevertheless I feel convinced that still other factors of more obscure nature have been of decisive importance. An analysis of the general immunological situation with respect to diphtheria in Sweden and some other European countries during recent years will lend support to this idea.

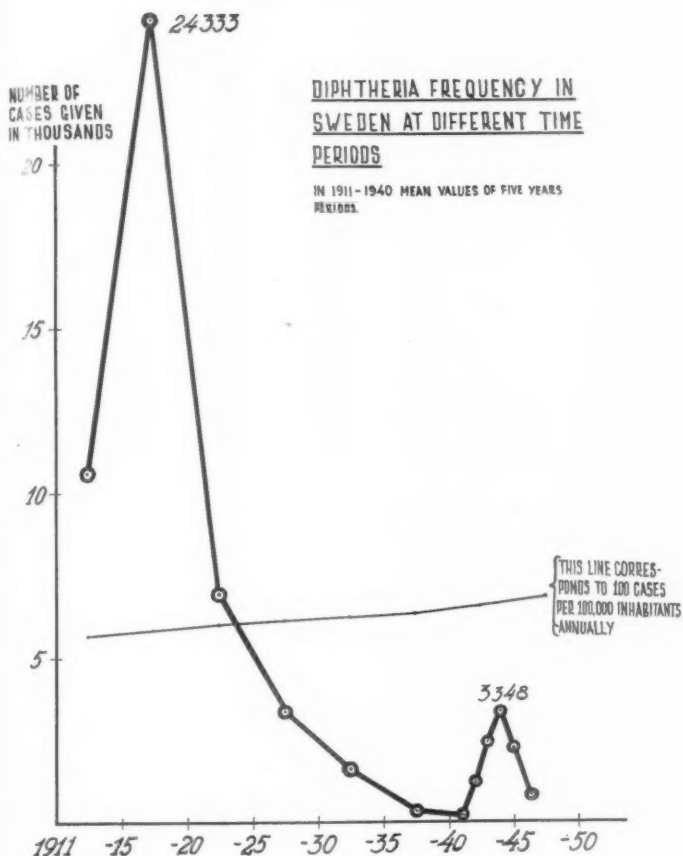


Figure 1.

At the time of the large-scale investigations of v. Gröer and Kassowitz (1919) and Zingher (1923) some twentyfive years ago, about 85 per cent of the adults investigated (in Vienna and New York) proved to be immune against diphtheria as judged from the antitoxin values of the blood or the Schick tests. In the dis-

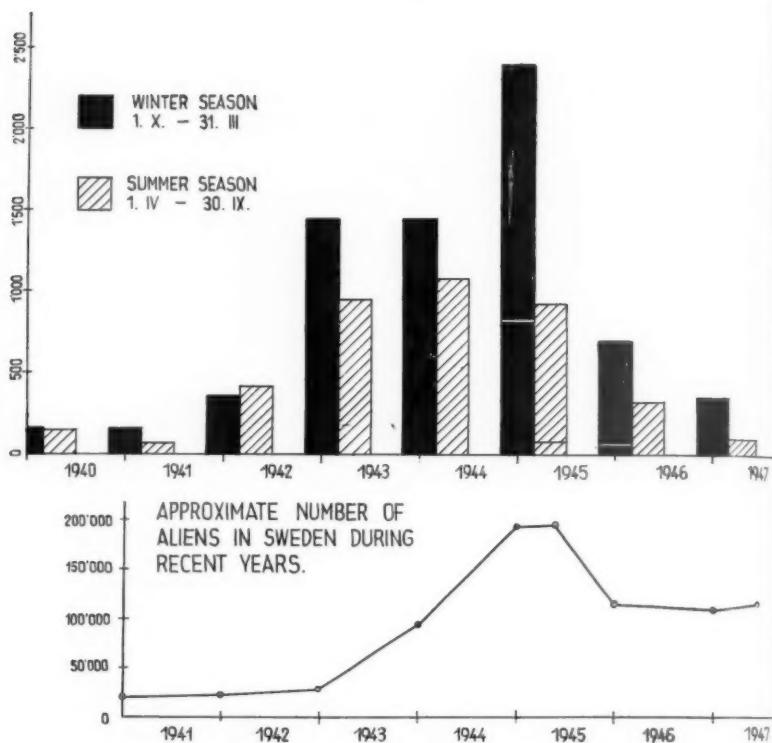


Figure 2. Number of cases of clinical diphtheria in Sweden in the forties. Winter and summer seasons given separately. Cross lines in some of the columns mean separate registration of cases in aliens [below the line] and natives [above the line].

cussion of immunity problems these results have remained unchallenged for many years.

The new diphtheria wave in the forties necessitated new large scale investigations of the susceptibility to diphtheria as a background for active immunization. The results demonstrated a complete change of the immunity situation as compared with that observed by the earlier workers. Already earlier, in 1936, Sigurjonsson had noted an extremely low percentage of Schick negative

Table 2.

The results of some investigations with Schick test from recent years as compared with the results of two often cited earlier investigations.

| AUTHOR | COUNTRY | YEAR OF INVEST. ¹⁾ | PERCENTAGE OF SCHICK NEG. INDIVIDUALS. NUMBER OF SUBJECTS INVESTIGATED IN BRACKETS. | | | | |
|-----------------------|----------------------|-------------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|
| | | | NEWBORNS | 1 YEAR | 7 YEARS | 14 YEARS | 20-30 YEARS |
| v. GRÖR AND KASSOWITZ | AUSTRIA (VIENNA) | 1919 | 84 ³⁾ (43) | 32 ³⁾ (28) | 38 ³⁾ (38) | 67 ³⁾ (27) | 84 ³⁾ (43) |
| ZINGHER | U.S.A. (NEW YORK) | 1921 | | | 56.5 (278) | 80.7 (2237) | |
| SIGURJONSSON | ICELAND (REYKYAVIK) | 1935 | | | — ¹⁾ (28) | — | |
| STRÖM | NORWAY (OSLO) | 1941 | | | — ¹⁾ (28) | — | 10.2 (22) |
| KOLLER | SWITZERLAND (ZÜRICH) | 1942 | | | | | 25 (22) |
| WRIGHT AND CLARK | ENGLAND (LONDON) | 1942-43 | APP. 50 (25) | | | | APP. 40 (25) |
| ERICSSON | SWEDEN (STOCKHOLM) | 1943 | | | — ¹⁾ (25) | — | 14 (22) |
| IPSEN | DENMARK (COPENHAGEN) | 1944 | | | | | APP. 40 (22) |
| VAHLQUIST AND PERSSON | SWEDEN (UPPSALA) | 1945 | 47 ³⁾ (32) | | | | 7 (85) |

¹⁾ Not always identical with the year of publication!

²⁾ Studied by means of antitoxin determination in the blood.

subjects among the school children of Reykyavik, Iceland. Some of the pertinent results are gathered in table 2.

The percentage figures in table 2 must of course be scrutinized with criticism. Even if the technique in performance of the Schick test has been carefully checked and standardized, the error arising from variations in the type of population investigated remains, especially that of social class and mode of lodging. The results from Vienna and New York are not directly comparable with those from Reykyavik or Zürich. Zingher clearly paid credit to such factors — »In various city hospitals we have tested groups of nurses, many of whom had only recently come to the city from smaller communities, and have found that among them from 50 to 75 per cent gave a positive reaction to the Schick tests» (p. 402 loc. cit.) — but subsequent authors have not always noted this, in referring to his work. The situation in this case has been very much the same as for the results of tuberculin tests. For many

years the high percentage figures of infected individuals found by Pirquet among the children of Vienna were assumed to be of general and permanent validity.

It can hardly be doubted, however, that the pronounced decrease of the number of Schick negative subjects in recent investigations also from comparatively big cities such as Stockholm and Oslo means a true change for the worse as to the general antitoxic immunity. In some cases this change of the immunological situation has been directly demonstrated in one and the same population (Stebbins et al., 1940; Bergman and Melin, 1944; Ipsen, 1946). The contradictory results of Eller and Phair from Baltimore (1941) might perhaps be explained by a factor of selection influencing the comparatively small group of non vaccinated children or special epidemic conditions.

The impairment of the general immunity situation is not *per se* surprising. It might be conceived as a natural consequence of the decreasing rate of diphtheria morbidity in so far as the natural immunity against diphtheria is the result of clinical and sub-clinical infections with the pathogenic microorganisms. In some cases, but certainly not in all, the unfavourable influence of malnutrition also on antibody formation (cf Cannon et al., 1943) must be considered. An observation will be discussed below, which might indicate, however, that the explanation is more complex than that given here.

Considering the unsatisfactory immunity situation in general it is not difficult to understand that the new diphtheria wave grew to fatal proportions in many countries such as the Netherlands, Norway and Finland. It is, on the other hand, amazing that it did not adopt the same disastrous character in every country, which had not for a long time demonstrated any great incidence of diphtheria. In Switzerland, Denmark and Sweden, for instance, there was an epidemic but it never became severe. Admitted that two of these countries were neutral and the third belonged to the less heavily damaged among the occupied countries, but sources of infection were never lacking, as mentioned above in regards to Sweden. And artificial immunization protected only part of the whole population.

The problem of immunity with respect to diphtheria is sometimes looked upon as mainly serological, a question of the presence or absence of antitoxic antibodies in the blood. Undoubtedly such a train of thought is incorrect. Virulent diphtheria bacilli obviously do not give rise to disease unless *two* different criteria are fulfilled

a. favourable growth conditions on the mucosa (sometimes skin) with which they come in contact and

b. absence of specific antibodies in protecting concentrations.

A Schick negative person is in many cases already by means of his antibody concentration or his ability of rapidly producing antibodies protected against diphtheria. (Sometimes, however, the antitoxin of the blood is protective only in concentrations materially exceeding that of the «Schick level», cf Ipsen, 1946). A Schick positive person lacks the serological defense mechanism but nevertheless he may be, temporarily or for a long time, resistant against diphtheric infection provided the growth conditions for the bacilli in the throat, nose and so on are unfavourable.

Too little interest was formerly attached to the question of the growth conditions for invading microorganisms on the mucosa of different body regions. Before and during the last war Dold and collaborators published several papers dealing with the inhibitory action of certain secretæ, i. e. the saliva, on the growth of certain pathogenic microorganisms, among them *C. diphtheriae*. Dold coined the term «Inhibine» for the inhibitory substances present, which were certainly not identical with the «lysozyme» of Fleming. In the discussion of the true nature of these «Inhibine» it was also emphasized (Weigmann and Hölzl, 1940) that there is a definite antagonism between various strains of streptococci on one side and certain pathological microorganisms such as the diphtheria bacilli on the other.

It seems quite reasonable to assume that the favourable course of the latest diphtheria epidemic in Sweden, in spite of the extremely unfavourable situation as concerns natural serological immunity, is explained by unfavourable growth conditions in a great number of subjects. In any case this explanation seems to me more probable than the alternative: namely, that the spreading

tendency of the bacteria from clinical cases and carriers should for some obscure reason be strongly reduced. I should furthermore like to raise the question whether the remarkably low diphtheria frequency in many countries during the pre-war decade and the resulting extremely poor serological immunity might not be explained in the same way.

This point of view might, perhaps, explain another otherwise amazing observation. In »Mitteilungen v. d. öffentl. Gesundheitsdienst» 1944 Klose and Prigge give a report of the results of diphtheria antitoxin titrations on a number of German soldiers. The material was admittedly limited, 87 subjects in all, and the results might therefore have been due to a mere chance. With this reservation it is, however, remarkable that 69 per cent of those investigated demonstrated an antibody concentration below 0.005 AU/cm^3 . Corresponding results were obtained by Wildführ in 1940. After many years of severe diphtheria the percentage of immunized subjects ought to have been high in Germany. In this case also unfavourable growth conditions for the diphtheria bacilli in the throat and nose might perhaps have exerted an influence by suppressing the number of carrier cases. The majority of naturally immunized subjects have acquired their immunity by means of »Stille Feiung». A successive change in the quota between clinical cases and carriers with reduction of the latter category might reduce the number of immune subjects even if there was an increase in clinical cases of the population.

Most interesting in this connections is an observation of Vogel-sang and Kryvi. In 1944 they found 67 per cent of Schick positive individuals among the adult population of Bergen in spite of the fact that a diphtheria epidemic had prevailed in the town for several years. In 3.307 immunized school children they found 1.8 per cent carriers. Ouchterlony in an investigation of Swedish school children in 1945 did not find a single diphtheria carrier among 1.300 subjects.

Investigations by Lewis (1941) and Wright and Clark (1944) indicate that also in England with high diphtheria frequency since a long time the numbers of Schick negative individuals in various age groups are definitely lower than the values of Zingher.

Table 3.

Diphtheria antitoxin levels in various age groups.
Unselected material from Sweden.

| AGE GROUP | NO OF PERSONS EXAMINED | ANTITOXIN LEVEL UNITS PER 6M ³ BLOOD SERUM | | | | | | ACCOUNT OF INDIVIDUAL ANTITOXIN VALUE IN THE GROUP ≥ 0.02 |
|--------------|------------------------|---|----------|----------------------|----------|-------------|----------|--|
| | | < 0.0005 | | $\geq 0.0005 < 0.02$ | | ≥ 0.02 | | |
| | | NO CASES | PER CENT | NO CASES | PER CENT | NO CASES | PER CENT | |
| ADULTS | 85 | 62 | 73 | 17 | 20 | 6 | 7 | $\frac{1}{2} < 20 < 10, \frac{1}{2} < 0.20 > 0.10, \frac{1}{2} < 0.10$ $\frac{1}{2} < 0.10 > 0.05, \frac{1}{2} < 0.05 > 0.02$ |
| NEWBORNS | 39 | 34 | 87 | 0 | 0 | 5 | 13 | $\frac{1}{2} < 0.40 > 0.20, \frac{1}{2} < 0.20 > 0.10$ $\frac{1}{2} < 0.05, \frac{1}{2} < 0.05 > 0.02, \frac{1}{2} < 0.02$ |
| 2-3 MOS. OLD | 15 | 14 | 93 | 1 | 7 | 0 | 0 | |
| 6-8 MOS. OLD | 15 | 14 | 93 | 1 | 7 | 0 | 0 | |
| TOTAL | 154 | 124 | 81 | 19 | 12 | 11 | 7 | |

The change of the immunological situation among adults is reflected among the children. The number of children immunized by infection from one year of age and upwards is very low. It might be assumed that the number of infants immunized by passive transfer of antibodies from their mothers during pregnancy would be reduced in proportion to the situation in adults.

In an investigation previously published (Vahlquist and Persson, 1945) the immunological situation in pregnant women and their offspring in Sweden has been subjected to a separate study by means of antitoxin determinations. The results of this investigation supplemented with some later analyses are shown in table 3.

The marked change of the immunological situation since the time of v. Gröer and Kassowitz and Zingher some twentyfive years ago is elucidated in two diagrams taken from the work cited above (Fig. 3 and 4).

The results of our exact antitoxin determinations (method of Claus Jensen) are of special interest in so far as they demonstrate

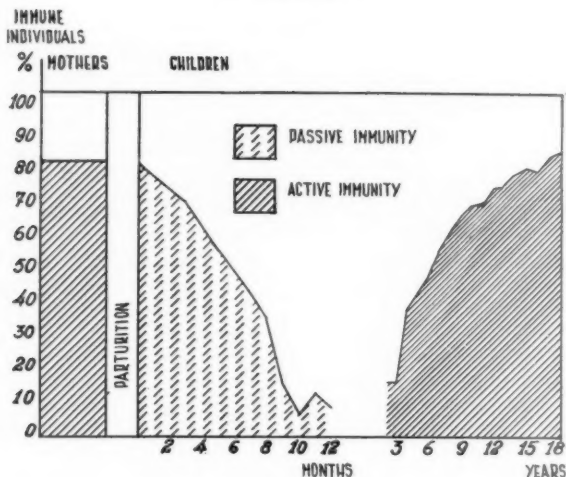


Figure 3. The immunity against diphtheria in New York children in the early twenties (Zingher 1923).

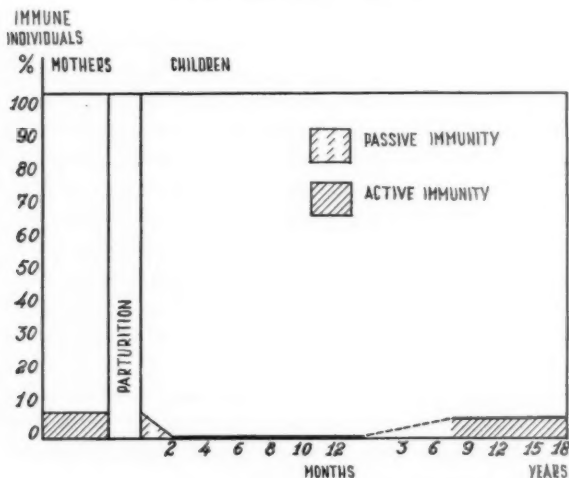


Figure 4. The immunity against diphtheria in Sweden at present in non-immunized individuals as judged from the Schick reaktion (Ericsson 1943) or from the antitoxin titre in blood (Vahlquist and Persson the 1945).

that the majority of individuals investigated not only have a low titer but actually reveal a complete lack of specific antibodies. In judging the results of active immunization this fact must be kept in mind — the results are not by far so good as in subjects with even a very low basic antitoxin level.

From a theoretical point of view it is of interest to note that the complete lack of antibodies in a great percentage of adult individuals rules out the theory of Hirszfeld that the antibodies at least to some extent might be the result of some serological «maturation process».

The following paper in this series deals with the results of active and passive immunization in infancy.

Summary.

The results from recent years of Schick tests and antitoxin determinations in the blood clearly demonstrate that the situation in regards to natural immunity against diphtheria nowadays is most unsatisfactory in many countries of Europe. In Sweden the number of Schick negative individuals among non-immunized adults does not exceed 10 %. As a consequence the newborns only infrequently demonstrate that passive immunity, which was formerly assumed to be the rule. In spite of the unfavourable immunological situation an epidemic of diphtheria in Sweden during the war rapidly subsided. Large scale immunization contributed to the outcome. The author forwards the theory that special conditions with respect to the growth conditions for the diphtheria bacilli in the throat might have been of even greater importance.

Résumé.

Les résultats obtenus pendant ces dernières années, de tests Schick et de déterminations d'antitoxine dans le sang, montrent clairement que la situation en ce qui concerne l'immunité naturelle contre la diphtérie est, de nos jours, fort peu satisfaisante dans bien des pays d'Europe. En Suède le nombre d'individus «Schick-négatifs» parmi les adultes non-immunisés n'excède pas 10 %. Il en résulte que les nouveaux-nés seulement dans des cas isolés

possèdent l'immunité passive qui, auparavant, était considérée générale. Malgré ca situation défavorable, une épidémie de diphthérie pendant la guerre cessa rapidement en Suède. Une immunisation en grande échelle contribuait à ce résultat. L'auteur expose la théorie que des conditions spéciales pour l'accroissement des bacilles de diphthérie dans la gorge pourraient avoir été d'une importance encore plus grande.

Zusammenfassung.

Die in den letzten Jahren bei Schick-Proben und Feststellung von Antitoxin im Blute erhaltenen Resultate zeigen, dass die natürliche Immunität heutzutage in vielen Ländern sehr gering ist. In Schweden sind unter den nicht immunisierten Erwachsenen nur 10 % Schicknegativ. In Folge dessen besitzen jetzt die Neugeborenen nur selten passive Immunität. Trotz dieser ungünstigen Verhältnisse war eine Diphtherie-Epidemie in Schweden während des Krieges rasch beendet, wozu eine im Grossen durchgeführte Immunisierung beitrug. Bestimmte Bedingungen sind für das Wachsen der Diphtherie-Bazillen im Halse wichtig.

Resumen.

Los resultados obtenidos con las pruebas Schick y las determinaciones de antitoxina en la sangre, efectuadas durante los últimos años, demuestran palpablemente que, en muchos de los países europeos, es hoy día muy poco satisfactoria la situación en lo que se refiere a inmunidad natural contra difteria. En Suecia el número de individuos «Schick negativos» entre adultos no inmunizados, no excede del 10 %. Los recién nacidos, por consiguiente, disfrutaban sólo raras veces de esta inmunidad pasiva que antiguamente se había creído que era una regla general. A pesar de esta desfavorable situación, durante la guerra fué sofocada rápidamente en Suecia una epidemia de difteria. A este excelente resultado contribuyó la inmunización en gran escala que se llevó a cabo. El autor defiende la teoría de que pueden haber tenido todavía mayor importancia las condiciones especiales relativas a las condiciones de desarrollo de los bacilos de la difteria en la garganta.

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Studies on Diphtheria.

II. Immunization against diphtheria in newborn babies and in infants.

By

BO VAHLQUIST, UNO MURRAY, and N. G. PERSSON.

For many years it has been considered a rule that about 85 per cent of all new born babies possess immunity against diphtheria owing to the transfer of specific antibodies from the mother during pregnancy, the duration of the immunity varying individually, but with an average of approximately 6 months. This view is maintained also in recent monographs such as the «Office Immunology» of 1947.

In part I of this series it was demonstrated (Vahlquist, 1948) that the rule cited above has now completely lost its general validity. Less than 10 per cent of all babies born in Sweden nowadays have protective antibody concentration in their blood. It can with certainty be said that the situation must be very much the same in many other countries, where the immunity situation among adults, *i. e.* also the mothers, has changed for the worse during the last decades (cf. Vahlquist *loc. cit.* table 2).

The facts related above make topical the question of immunization in early infancy. For the time being different principles are practised in different countries. In Sweden, for instance, it is recommended to begin vaccination only when the child is one year of age.¹ In the United States the Academy of Pediatrics has recommended to begin at nine months of age but actually immunization is often performed already at six months. This might to some extent be due to the fact that combined vaccinations with

¹ Addendum: In a paper of Nov. 17 1947 the Swedish Medical Board recommends vaccination against diphtheria after six months of age.

diphtheria, pertussis and tetanus are carried out on a large scale, and the necessity of an early pertussis-vaccination is undisputed.

The situation to-day concerning diphtheria immunity enhances the desirability to establish, if possible, satisfactory protection already from birth. The possibility cannot be excluded that infants also without protecting antibodies in their blood may be less susceptible to diphtheria, perhaps due to unsatisfactory growth conditions for the bacilli in the nose and throat. But nevertheless there is a risk of attracting the disease in this age also, and the outcome is not seldom fatal. During the last diphtheria wave in Sweden several small epidemics occurred among newborns and small infants, all with a high mortality.

It is thus quite obvious that immunization already in early infancy is highly desirable. But is it practicable? Most authors, among them Rohmer (1914), Blum (1932), Jakobkiewicz (1937), McKhann and Kopnick (1938) deny this question.

We have not felt convinced of the argumentation concerning the claimed inefficiency of diphtheria immunization at an early age. We have attacked the problem with an exact technique and have, as will be shown below, come to quite different results.¹

Provided that small infants are apt to react on active immunization, there will be, nevertheless, just as in every immunization procedure, an initial period without protection. Theoretically it would seem possible to overbridge this period by means of immunizing the mothers during pregnancy in the hope of thereby transferring antibodies to the offspring, protecting it during the first period of life. We have also performed such a series of experiments.

The mode of action has therefore been the following:

A. Immunization of infants belonging to different age groups from the newborn period and upwards.

B. Immunization of pregnant women and control of the effect on their offspring.

¹ One of the authors (B. V.) gave a preliminary report of the results at the eighth northern paediatric congress in Helsingfors, June 1946 (*Acta Paed.* 35, p. 260).

Technique. The antitoxin determinations were performed according to the method worked out by Claus Jensen (1933). This technique is highly sensitive and very accurate. Usually the titration was continued to a limit of 0.0005 antitoxic units (A. U.) per cc, in some cases even down to 0.00005 A. U./cc.

Material. The children and women treated were all under control of the Welfare Center of the Academic Hospital at Uppsala.

Aluminium precipitated standard diphtheria toxoid from the State Bacteriological Laboratory in Stockholm was in use throughout. The strength of the vaccine is given as 45 flocculation units per cc. The mode of preparation was described by Ericsson (1946).

The *children* were immunized with single injections of 1.0 cc of the vaccine. Three different age groups were chosen: newborns (usually immunized on the first or second day of life), infants from 2 to 3 months and 6 to 8 months of age. Each group comprised about 15 children. The antitoxin concentration was determined before immunization as well as one and three months afterwards, in some cases after the lapse of about six or twelve months also. One of the children developed a generalized punctate erythema in combination with fever of medium grade about 12 hours after the injection. None of the others showed any general reactions. On the site of the injection small infiltrates were often noted, large infiltrates or even abscess formation were not observed.

The *women* were immunized during the last two or three months of gestation. The following schedule was practised. 0.2 cc vaccine — four weeks interval — 0.5 cc vaccine — and in part of the cases four weeks interval and 0.5 cc vaccine. With two exceptions (K-e, 34, and M-n, 25) the patients had all received the second injection at least two weeks before parturition. Most of the women were between 20 and 30 years of age. A selection was made merely in that women were immunized only when they demonstrated a negative Schick *control* reaction. With these precautions serious reactions were never noted. The antitoxin concentration was determined before vaccination and at parturition. From the child blood samples for analysis were taken at birth as well as one or several times later, during the first year of life.

Table 1.

Immunization of infants. Single injection of 1.0 cm³ precipitated toxoid.

1: Newborn infants.

| PATIENT | AGE | BEFORE IMMUNIZATION | AFTER IMMUNIZATION | | | | | |
|---------|---------|------------------------|-----------------------------|--------------------|------------------------------|--------------------|--------------------------|--------------------|
| | | AU/CM ³ | INTERVAL (ABOUT 1 MONTH) | AU/CM ³ | INTERVAL (ABOUT 3 MONTHS) | AU/CM ³ | INTERVAL (5-7 MONTHS) | AU/CM ³ |
| E-D | NEWBORN | < 0.0005 | 5 WE. | < 0.20 > 0.10 | 13 WE. | < 0.05 > 0.02 | — | — |
| L-D | — | < 0.0005 | 4½ WE. | < 0.20 > 0.10 | 13 WE. | < 0.05 > 0.02 | — | — |
| A-N | — | < 0.0005 | 4½ WE. | < 0.10 | 13 WE. | = 0.02 | — | — |
| A-N | — | < 0.0005 | 5 WE. | = 0.004 | 13 WE. | < 0.01 > 0.005 | 22 WE. | < 0.05 > 0.02 |
| S-N | — | < 0.0005 | 5 WE. | = 0.002 | 16 WE. | < 0.02 > 0.001 | 28 WE. | < 0.05 > 0.02 |
| H-N | — | < 0.0005 | 5½ WE. | = 0.001 | — | — | 29 WE. | < 0.10 > 0.05 |
| L-W | — | < 0.0005 | 4 WE. | = 0.001 | 13 WE. | < 0.05 > 0.02 | — | — |
| M-W | — | < 0.0005 | 4 WE. | < 0.0005 | 13 WE. | = 0.02 | 28 WE. | < 0.05 > 0.02 |
| E-N | — | < 0.0005 | 5 WE. | < 0.0005 | 13 WE. | < 0.05 > 0.02 | 25 WE. | < 0.05 > 0.02 |
| I-N | — | < 0.0005 | 5 WE. | < 0.0005 | 13 WE. | = 0.01 | 30 WE. | < 0.05 > 0.005 |
| J-N | — | < 0.0005 | 4½ WE. | < 0.0005 | — | — | — | — |
| G-N | — | < 0.0005 | 4½ WE. | < 0.0005 | 12 WE. | < 0.005 > 0.004 | 29 WE. | < 0.005 > 0.005 |
| H-T | — | < 0.0005 | 4½ WE. | < 0.0005 | 12 WE. | = 0.004 | — | — |
| E-M | — | < 0.0005 | 6½ WE. | < 0.0005 | 13 WE. | < 0.005 > 0.003 | 24 WE. | < 0.02 > 0.01 |
| J-N | — | < 0.0005 | 4 WE. | < 0.0005 | 13 WE. | < 0.20 > 0.10 | 24 WE. | < 0.10 > 0.05 |
| MEDIAN | | < 0.0005 | 4½ WE. | < 0.0005 | 13 WE. | = 0.02 | 28 WE. | < 0.05 > 0.02 |

Results.

A. Immunization of infants by vaccination.

The results of immunization with single injections of diphtheria vaccine in the different age groups are collected in table 1, 2 and 3 and summarized in table 4. Three typical cases are recorded graphically in figure 1.

The classification in three titer groups in some of the tables of this series aims at the following distinction: one group of «antitoxin free» individuals (< 0.0005 A.U./cc), one group of individuals with diphtheria antitoxin in «protective» concentrations (\geq 0.02 A.U./cc) and a third group between these (\geq 0.0005 < 0.02 A.U./cc). According to v. BEHRING (1914) the protective concentration of antitoxin is $1/100$ — $1/20$ fach normalen Blutantitoxingehalts. It is, however, obvious that the minimal

Table 2.

Immunization of infants. Single injection of 1.0 cm³ precipitated toxoid.

2: Infants 2—3 months old.

| PATIENT | AGE | BEFORE IMMUNIZATION | AFTER IMMUNIZATION | | | | | |
|---------|---------|------------------------|-----------------------------|--------------------|------------------------------|--------------------|--------------------------|--------------------|
| | | AU/CM ³ | INTERVAL (ABOUT 1 MONTH) | AU/CM ³ | INTERVAL (ABOUT 3 MONTHS) | AU/CM ³ | INTERVAL (5-7 MONTHS) | AU/CM ³ |
| L-N | 2 M | < 0.0005 | 4 WE. | < 0.10 | — | — | — | — |
| V-N | 2 M | < 0.0005 | 5 WE. | < 0.10 > 0.05 | 14 WE. | < 0.10 > 0.05 | 36 WE. | < 0.20 > 0.10 |
| C-R | 3 M | < 0.0005 | 4 WE. | < 0.10 > 0.05 | 14 WE. | < 0.10 > 0.05 | — | — |
| K-N | 2 3/4 M | < 0.0005 | 4 WE. | < 0.10 > 0.05 | 12 WE. | < 0.05 > 0.02 | — | — |
| O-N | 2 1/2 M | < 0.0001 | 5 WE. | < 0.05 > 0.02 | — | — | — | — |
| E-D | 2 1/2 M | < 0.0005 | 5 1/2 WE. | < 0.05 > 0.02 | 13 WE. | < 0.05 > 0.02 | — | — |
| E-U | 2 1/2 M | < 0.0005 | 7 1/2 WE. | < 0.05 > 0.02 | 15 WE. | < 0.05 > 0.02 | — | — |
| S-L | 2 3/4 M | < 0.0005 | 6 WE. | < 0.02 > 0.01 | 13 WE. | < 0.02 > 0.01 | 35 WE. | < 0.05 > 0.02 |
| H-N | 3 M | < 0.0005 | 5 1/2 WE. | < 0.02 > 0.01 | 22 WE. | < 0.01 > 0.005 | 36 WE. | < 0.20 > 0.10 |
| B-D | 3 1/4 M | < 0.0005 | 4 WE. | < 0.01 > 0.005 | 12 WE. | < 0.01 > 0.005 | 29 WE. | < 0.05 > 0.02 |
| N-G | 2 1/2 M | < 0.0005 | 4 WE. | < 0.005 > 0.003 | — | — | — | — |
| H-N | 2 1/2 M | < 0.0005 | 4 1/2 WE. | < 0.003 > 0.002 | 12 WE. | < 0.01 > 0.005 | — | — |
| L-M | — | < 0.0005 | — | < 0.003 > 0.002 | — | — | — | — |
| E-N | 2 M | < 0.0005 | 4 WE. | < 0.002 > 0.001 | — | — | — | — |
| J-N | 2 3/4 M | < 0.0005 | 4 1/2 WE. | < 0.0005 | 13 WE. | < 0.003 > 0.002 | 24 WE. | < 0.05 > 0.02 |
| MEDIAN | 2 1/2 M | < 0.0005 | 4 1/2 WE. | < 0.02 > 0.01 | 13 WE. | < 0.02 | 35 WE. | < 0.05 > 0.02 |

protective concentration is greatly varying, and at least in some epidemics materially exceeding the value given by v. BEHRING (cf. IPSEN 1946). The value 0.02 A.U./cc corresponds roughly to that given by JENSEN (1931) warranting without exception a negative Shick reaction.

The results given in the tables clearly show that infants during the first six months of life and even in the newborn period *do* react with antibody formation after immunization. The effect seems to be delayed in the newborn babies but the final titer reached is of the same magnitude in all groups and does not deviate obviously from that observed in antitoxin-free adults. Admittedly the dose of antigen is, however, relatively larger in the low age groups, as one cubic centimeter of vaccine was given in all groups irrespective of age.

Table 3.

Immunization of infants. Single injection of 1.0 cm³ precipitated toxoid.

3: Infants 6—8 months old.

| PATIENT | AGE | BEFORE IMMUNIZATION | AFTER IMMUNIZATION | | | | | |
|---------|------|------------------------|-----------------------------|--------------------|------------------------------|--------------------|--------------------------|--------------------|
| | | AU/CM ³ | INTERVAL (ABOUT 1 MONTH) | AU/CM ³ | INTERVAL (ABOUT 3 MONTHS) | AU/CM ³ | INTERVAL (5-7 MONTHS) | AU/CM ³ |
| L-N | 7 M. | <0.0005 | 7 WE | <0.20 >0.10 | — | — | — | — |
| V-M | 6 M | <0.0005 | 4 WE | <0.10 >0.05 | 12 WE. | <0.40 >0.20 | — | — |
| E-D | 6½ M | <0.0005 | — | — | 15 WE. | <0.10 >0.05 | 40 WE. | <0.01 >0.005 |
| H-R | 5 M | <0.0005 | 4½ WE. | <0.05 >0.02 | 15 WE. | <0.05 >0.02 | 26 WE. | <0.05 >0.02 |
| H-N | 6½ M | <0.0005 | 5 WE. | <0.05 >0.02 | 17 WE | <0.05 >0.02 | — | — |
| L-N | 7 M | <0.0005 | 8 WE. | <0.05 >0.02 | 21 WE. | <0.05 >0.02 | — | — |
| J-G | 8½ M | <0.0005 | 5 WE | <0.05 >0.02 | — | — | — | — |
| S-D | 6½ M | <0.0005 | 4½ WE. | <0.05 >0.02 | — | — | — | — |
| H-N | 7 M | <0.0005 | 4 WE | <0.02 >0.01 | 12 WE. | <0.05 >0.02 | 25 WE | <0.10 >0.05 |
| J-N | 6½ M | <0.0005 | 4 WE | <0.02 >0.01 | 14 WE. | <0.02 >0.01 | 35 WE | <0.05 >0.02 |
| N-G | 7 M | <0.0005 | 4 WE | <0.02 >0.01 | — | — | — | — |
| F-L | 7½ M | <0.0005 | 5 WE | =0.01 | 14 WE. | <0.05 >0.02 | 41 WE. | <0.01 >0.02 |
| N-D | 7½ M | <0.0005 | 4½ WE | <0.01 >0.005 | — | — | — | — |
| B-T | 7½ M | <0.0005 | 4½ WE. | <0.01 >0.005 | — | — | — | — |
| N-B | 7 M | <0.0005 | 4 WE | <0.002 | 13 WE | <0.02 >0.01 | 29 WE. | <0.02 >0.01 |
| E-N | 7½ M | <0.0005 | 4½ WE | <0.0005 | 7½ WE | <0.004 >0.005 | — | — |
| MEDIAN | 7 M | <0.0005 | 4½ WE | =0.02 | 14 WE | <0.05 >0.02 | 32 WE | =0.02 |

The comparatively good reaction observed even in the new-born group is at variance with the results of earlier investigators. The possible explanation of these divergent findings will be discussed below.

B. Immunization during gestation.

In all 27 women were treated. All of these received two (17 cases) or three (10 cases) injections of vaccine according to the schedule given above. The antitoxin concentrations achieved through the vaccination were really high in those two women only, who had a certainly very low but nevertheless measurable antitoxin concentration in their blood already before immunization.

Table 4.

The effect of immunization against diphtheria in various periods of infancy as compared with that of a control group of older children and adults.

| AGE GROUP | NO. OF SUBJECTS IMMUNIZED | TIME OF TESTING | ANTITOXIN LEVEL UNITS PER CM ³ BLOOD SERUM | | | |
|-----------------------------------|------------------------------|---------------------------------|---|--------------------|--------|-----------------|
| | | | < 0,0005 | ≥ 0,0005 < 0,02 | ≥ 0,02 | MEDIAN VALUE |
| NEWBORNS | 15 | BEFORE IM- MUNIZATION | 15 | 0 | 0 | < 0,0005 |
| | | AFTER IM- MUNIZATION 1 MONTH | 8 | 4 | 3 | < 0,0005 |
| | | → 3 MOS. | 0 | 6 | 7 | = 0,02 |
| | | → 6 → | 0 | 3 | 6 | < 0,05 > 0,02 |
| 2-3 MONTHS OLD | 15 | BEFORE IM- MUNIZATION | 15 | 0 | 0 | < 0,0005 |
| | | AFTER IM- MUNIZATION 1 MONTH | 0 | 8 | 7 | < 0,02 > 0,01 |
| | | → 3 MOS. | 0 | 5 | 5 | = 0,02 |
| | | → 6 → | 0 | 1 | 4 | < 0,05 > 0,02 |
| 6-8 MONTHS OLD | 15 | BEFORE IM- MUNIZATION | 15 | 0 | 0 | < 0,0005 |
| | | AFTER IM- MUNIZATION 1 MONTH | 1 | 7 | 7 | = 0,02 |
| | | → 3 MOS. | 0 | 2 | 7 | < 0,05 > 0,02 |
| | | → 6 → | 0 | 3 | 3 | = 0,02 |
| OLDER CHILD- REN AND ADULTS | 14 | BEFORE IM- MUNIZATION | 14 | 0 | 0 | < 0,0005 |
| | | AFTER IM- MUNIZATION 1 MONTH | 1 | 5 | 8 | < 0,05 > 0,02 |
| | | | | | | |
| | | | | | | |

In general the rise of the antitoxin was moderate. In seven cases, all of them treated with two injections only, the immunity level, taken as 0.02 A. U./cc. serum, was never reached and in one of these cases no reaction at all could be demonstrated (cf. table 5).

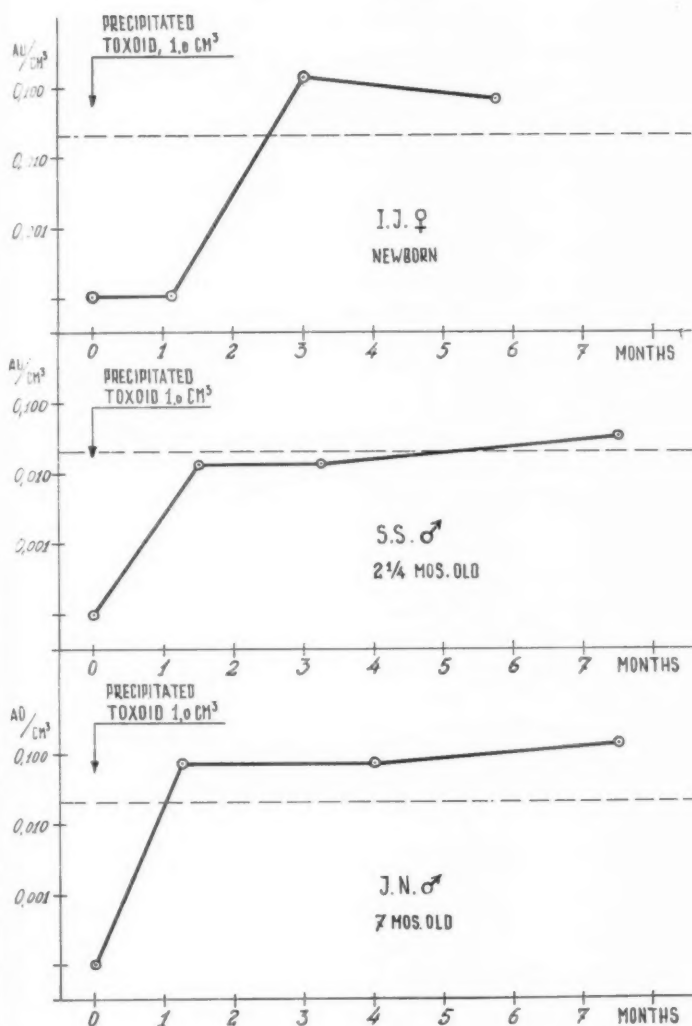


Figure 1. Antitoxin response to immunization against diphtheria in different periods of infancy.

Table 5.

Immunization against diphtheria in pregnant women in order to protect the offspring.

| PATIENT | AGE YEARS | NUMBER OF INJECTIONS OF TOXOID | ANTITOXIN LEVELS | | |
|------------------|--------------|---|------------------------|-------------------|-------------------|
| | | | MOTHER | | CHILD |
| | | | BEFORE IMMUNIZATION | AT PARTURITION | AT PARTURITION |
| L-G | 35 | 2 | $< 0,004$ $> 0,005$ | $< 20 > 10$ | $< 20 > 10$ |
| K-E | 34 | 2 | $< 0,005 > 0,002$ | $< 16 > 14$ | $< 14 > 12,5$ |
| V-G | 25 | 3 | $< 0,0005$ | $< 1,6 > 1,0$ | $= 0,40$ |
| N-M | 29 | 3 | $< 0,0005$ | $< 0,80 > 0,40$ | $< 1,60 > 0,80$ |
| S-G | 19 | 3 | $< 0,0005$ | $< 0,80 > 0,40$ | $< 0,40 > 0,20$ |
| J-R | 23 | 2 | $< 0,0005$ | $< 0,80 > 0,40$ | $< 0,40 > 0,20$ |
| F-K | 25 | 2 | $< 0,0005$ | $< 0,80 > 0,40$ | $< 0,20 > 0,10$ |
| S-G | 19 | 3 | $< 0,0005$ | $= 0,40$ | $< 0,40 > 0,20$ |
| L-G | 44 | 2 | $< 0,0005$ | $= 0,40$ | $< 0,20 > 0,10$ |
| N-M | 24 | 3 | $< 0,0005$ | $< 0,40 > 0,20$ | $= 0,40$ |
| H-D | 32 | 2 | $< 0,0005$ | $< 0,40 > 0,20$ | $= 0,20$ |
| L-N | 24 | 3 | $< 0,0005$ | $< 0,40 > 0,20$ | $= 0,20$ |
| F-G | 27 | 3 | $< 0,0005$ | $< 0,40 > 0,20$ | $< 0,20 > 0,10$ |
| V-N | 21 | 3 | $< 0,0005$ | $= 0,20$ | $< 0,10 > 0,05$ |
| L-N | 32 | 3 | $< 0,0005$ | $< 0,20 > 0,10$ | $= 0,20$ |
| P-N | 29 | 3 | $< 0,0005$ | $< 0,20 > 0,10$ | $< 0,20 > 0,10$ |
| K-N | 23 | 2 | $< 0,0005$ | $= 0,10$ | $< 0,05 > 0,03$ |
| N-D | 25 | 2 | $< 0,0005$ | $< 0,10 > 0,05$ | $< 0,10 > 0,05$ |
| A-N | 24 | 2 | $< 0,0005$ | $< 0,10 > 0,05$ | $< 0,05 > 0,02$ |
| B-N | 27 | 2 | $< 0,0005$ | $< 0,05 > 0,02$ | $< 0,0005$ |
| A-N | 27 | 2 | $< 0,0005$ | $< 0,02 > 0,01$ | $< 0,0005$ |
| L-N | 27 | 2 | $< 0,0005$ | $< 0,005 > 0,003$ | $= 0,001$ |
| L-G | 26 | 2 | $< 0,0005$ | $< 0,005 > 0,005$ | $< 0,0005$ |
| M-N | 25 | 2 | $< 0,0005$ | $< 0,005 > 0,005$ | $< 0,0005$ |
| O-N | 22 | 2 | $< 0,0005$ | $< 0,005 > 0,001$ | $< 0,0005$ |
| J-D | 27 | 2 | $< 0,0005$ | $= 0,001$ | $= 0,001$ |
| K-N | 19 | 2 | $< 0,0005$ | $< 0,0005$ | $< 0,0005$ |
| | | | | | |
| MEDIAN VALUES | 29 | | $< 0,0005$ | $= 0,20$ | $< 0,20 > 0,10$ |

Already v. Gröer and Kassowitz (1915) demonstrated that there is on the whole usually a good agreement between the antitoxin concentration of naturally immunized women and their offspring. *A priori* it seems quite reasonable to assume that this also should be the case after artificial immunization. The results of our investigations confirm this assumption. The titer values in the mothers and their children corresponded very well, with only a slight tendency towards lower values in the latter.

For practical reasons the continued control of the children could not be carried out at regular intervals. In all except five subjects, however, one to three determinations of the antitoxin concentrations of the blood were made between three and twelve months of age. It is only natural that the values thereby observed were correlated to the initial values at birth. Those children who then had an antitoxin concentration at or above 0.02 A. U./cc. demonstrated without exception measurable antitoxin concentration three to nine months later on, relatively seldom, however, the values still were above the «immunity level», 0.02 A. U./cc. The children with very high initial concentrations after eight to nine months still demonstrated such satisfactory values as $<0.80 >0.40$ and $<0.20 >0.10$ A. U./cc. respectively (cf table 6).

In nineteen children of this group immunization with a single injection of 1.0 cc. vaccine was performed after the second antitoxin determination; and four to seven weeks later on an additional third determination. The purpose of this experiment was to determine whether the presence of passively transferred antibodies interferes with the action of active immunization. The results are assembled in table 6.

The results given in table 6 make evident that there is a border line antitoxin level between 1/10 and 1/50 antitoxin unit per cc. *Over* this level active immunization seems to be completely without immunizing effect; *below* this level the effect is just as good as in subject who have completely lost their antibodies. Those two cases just within the border line undoubtedly show a reaction, but it is relatively weak and at the same time slow. The slow reaction may depend upon the fact that these both cases were newborns, but might also be due the fact that the effect could set

Table 6.

The effect of immunization in infants with persisting passive antibodies.

| SUBJECT | AT PARTURITION | BEFORE IMMUNIZATION | | AFTER IMMUNIZATION | |
|---------|-----------------|---------------------|------------------|--------------------|-----------------------------|
| | A.U./KBCM | AGE IN MONTHS | A.U./KBCM | INTERVAL IN WEEKS | A.U./KBCM |
| K-E | < 14 > 12.5 | 8 | < 0.80 > 0.40 | 4 1/2 | = 0.40 |
| A-D | < 0.40 > 0.20 | NEWBORN | < 0.40 > 0.20 | 4 1/2 | < 0.20 > 0.10 ^y |
| L-G | < 20 > 10 | 8 1/2 | < 0.20 > 0.10 | 4 1/2 | < 0.05 > 0.02 |
| N-M | < 1.60 > 0.80 | 4 1/4 | < 0.20 > 0.10 | 4 1/2 | < 0.05 > 0.02 |
| H-D | < 0.20 > 0.10 | 1 1/4 | < 0.20 > 0.10 | 4 1/2 | < 0.02 |
| N-N | < 0.05 > 0.02 | NEWBORN | < 0.05 > 0.02 | 4 1/2 | < 0.05 > 0.02 ^y |
| J-N | < 0.05 > 0.02 | NEWBORN | < 0.05 > 0.02 | 5 1/2 | < 0.01 > 0.005 ^y |
| F-G | < 0.20 > 0.10 | 4 1/4 | < 0.02 > 0.01 | 5 1/2 | = 0.10 |
| N-M | = 0.40 | 4 1/2 | < 0.01 > 0.005 | 5 | = 0.40 |
| S-G | < 0.40 > 0.20 | 5 | < 0.01 > 0.005 | 4 1/2 | < 0.80 > 0.40 |
| W-E | < 0.005 > 0.002 | NEWBORN | < 0.005 > 0.002 | 4 1/2 | = 0.01 ^y |
| N-D | < 0.10 > 0.05 | 7 1/2 | = 0.002 | 7 | < 0.10 > 0.05 |
| J-R | < 0.40 > 0.20 | 7 | < 0.005 > 0.001 | 4 1/2 | = 0.05 |
| M-N | — | 7 1/2 | < 0.005 > 0.001 | 5 1/2 | < 0.20 > 0.10 |
| V-N | < 0.10 > 0.05 | 5 | < 0.005 > 0.001 | 7 | = 0.20 |
| H-D | = 0.20 | 9 1/4 | < 0.002 > 0.001 | 6 | = 0.20 |
| L-N | = 0.20 | 4 1/2 | = 0.001 | 5 1/2 | < 0.10 > 0.05 |
| V-G | = 0.40 | 4 | < 0.001 > 0.0005 | 4 | < 0.20 > 0.10 |
| N-G | > 0.02 | 7 | < 0.001 > 0.0005 | 4 1/2 | < 0.10 > 0.05 |

^y 15 WE = 0.05; 27 WE < 0.01 > 0.005 ^y 28 WE < 0.05 > 0.02;

21 WE < 0.10 > 0.05; ^y 13 WE < 0.02 > 0.005; 29 WE < 0.05 > 0.02;

^y 24 WE < 0.05 > 0.02.

in only after the titer of the passive antibodies had decreased furthermore.

The possibility cannot be excluded that after vaccination of the mothers also antigen may have been transferred to the foetus. The results of vaccination of the children later on (table 6) might give some support to such a view. In eleven subjects who were beyond the newborn period and demonstrated a passive antitoxin concentration below 0.02 A. U./cc. the titer rose in about one month after the vaccination to a median value of $<0.20>0.10$ A. U./cc as compared with 0.02 A. U./cc in a control group (cf table 3). If this observation comes true in larger materials it must be explained as a «secondary stimulus» effect. Nevertheless it is clear that the antibodies present in the child at birth must be mainly passive in origin, the concentration in mother and child is practically equal at birth and after birth the antibodies subside rather rapidly in the child.

Discussion. The view is broadly accepted that in infants during the first period of life the antibody producing power is unsatisfactory whence immunization, for instance against diphtheria, should be of little value. The arguments presented for such an opinion do not, however, seem altogether convincing when scrutinized more closely. As regards diphtheria it has been a disadvantage that formerly the number of antitoxin-free children during the first period of life were in minority. Suitable objects for immunization, therefore, were few in number and the whole question seemed to be of minor importance due to the widespread protection through passive antibodies.

As for other diseases, *i. e.* small pox, some earlier investigations seem to indicate that the result of immunization are less satisfactory in newborn children as compared with children more than six months of age. But in this case there is little doubt that also the newborn babies do react on immunization even if the effect is of shorter duration (Donnally and Nicholson, 1934). Furthermore it is quite clear that BCG immunization provokes tuberculin allergy and therefore probably also immunity in newborn babies much in the same manner as in older children and adults (Rydén, 1946).

Quite recently Sako (1947) in immunizing children from 2 weeks to 3 months old with aluminium precipitated toxoid against whooping cough observed just as good results as in older age groups.

The results of our investigations demonstrate that immunization against diphtheria with aluminium precipitated toxoid is effective already in newborn babies. A comparison between the different age groups chosen, newborns and infants two to three months and six to eight months old, does not show a palpable difference with respect to the end results after administration of one and the same quantity of antigen.

In one respect, however, the effect of immunization differs markedly in the newborn group. One month after the immunization only 7 out of 15 children had achieved a measurable concentration of antitoxin in their blood, whereas the children of the two other groups almost unanimously had reacted by that time. Still, the values after three months corresponded fairly well in all groups. It may be that the antigenic effect in the newborn group was slowed down all through or that the effect asserted itself only after an initial period of more or less complete refractivity.

How may these results, contradictory to those of earlier investigators, be explained? Probably the type of vaccine used in immunization is relevant the antigenic effect of the precipitated toxoid being much more protracted than that of the fluid toxoid. Apart from this we believe, however, that previous investigators have been misled through one or several of the following errors:

a. They have not been aware of the markedly *slow* reaction in the newborn babies.

b. They have compared the results of immunization in young infants with that of older children and adults. Formerly this latter group must have comprised a rather large number of potentially immune subjects. The vaccination then acted as a secondary stimulus and was far more potent than in the infants who were not in possession of such a basic immunity. In other words the reactive power was not compared on the same grounds.

c. The inhibitory action on the result of the active immunization, owing to the persistence of «passive» antibodies received from the mother, has not been considered.

The series of earlier investigators are therefore unsatisfactory in gauging the real *ability* of the organism to react with antibody formation on the *first antigenic stimulus*. The results here presented clearly demonstrate that this ability is present already in the newborn babies, in children two to three months of age neither the rapidity nor the degree of reaction differing materially from that in older children and adults immunized with one and the same quantity of vaccine.

It is accordingly possible to immunize even newborn babies against diphtheria. Still there is always in immunization procedures a period of latency before the effect is attained. In the newborn babies this period is often prolonged, a fact which might explain the observation that malignant diphtheria in infants is especially found in the first month of life. Is it possible to overbridge this period of non-protection by vaccination the mothers during pregnancy?

Ribadeau—Dumas (1925) was not successful in trying to immunize the children from their mothers but Sorrentino (1931) claimed to have found a satisfactory response in the offspring. The methods used in these experiments were not by far as accurate as that of Claus Jensen. Technical shortcomings may explain observations of the type that the antibody concentration of the child sometimes was reported to be essentially more elevated than that of the mother. Only after the completion of our investigation in 1946 did we gain access to the work of Liebling and Schmitz (1943) published in the United States during the war. In a comparatively large material of women, most of whom had a basic immunity before the immunization, they were able to demonstrate to full evidence that the increase of titer was reflected in the blood of the offspring. Furthermore they followed the successive decrease of the titer values after birth.

Our results clearly show, as do those of Liebling and Schmitz, that immunization of the offspring by means of vaccinating their mothers during pregnancy is perfectly feasible. Might this become a method of choice in the event of a new threat of diphtheria? To answer this question it is necessary to scrutinize the problem from different angles.

The first pre-requisite is of course that the immunization is definitely innocuous to the mother and the foetus. Our material is composed mainly of women below 30 years of age. It is a well known fact that side reactions become more and more common with the increasing age of the test subject. The *control* reactions according to Schick often predict such an untoward reaction. In our material only women with negative control reactions were included. This means a limitation of applicability, which might, however, be less important with access to the new «purogenated» toxoids (Lederle).

Another important question is the following. How does the passive immunity interfere with the active immunization? That is just as important to settle whether the passive immunity is acquired from the mother or the result of serum treatment. The problem occurs in the sometimes adapted «combined prophylaxis» with antitoxin and toxoid at the same time in case of immediate threat of diphtheria. The opinions have been divergent as to the possible interference. Ramon (1938) advocated that the toxoid acted just as well as if given alone. But Downie et al. (1941) hold an opposite view, seemingly on good reasons.

The special problem of the possible interference with the immunization of the «passive» (homologous) antibodies in the newborn infant has, as far as we know, been dealt with only by Greengard and Bernstein (1935). Their results of repeated Schick tests indicated that the effect of immunization was unsatisfactory as long as the infants were Schick negative from passively transferred antibodies. Our results from quantitative determinations of the antibody concentration elucidate the question in a more accurate way (table 6). They show that there is a border line zone between 1/10 and 1/50 A. U./cc. Above this zone the effect of immunization was completely inhibited, below the lower limit the effect was just as good as that in the complete absence of antibodies.

It is of interest to note that the border line zone discussed above corresponds fairly well with the «immunity level». It is reasonable to assume, however, that the position of the zone depends on the quantity of antigen administered.

Summing up, the results here demonstrated show that it is

possible to protect infants, and especially infants less than six months old, by way of passive immunization *via* the mother as well as through active immunization of the child itself. Which should be the method of choice?

Passive immunization via the mother has the disadvantage that the protection, at least in our present immunological status in Sweden with a frequently complete lack of basic immunity, is not quite regularly achieved and in any case usually gives a protection of short duration only. Furthermore it is necessary to perform a Schick *control* test in advance in order to avoid untoward reactions, unless «purogenated» toxoids are used.

Active immunization has the disadvantage that it gives effect often only after the lapse of a few months in the newborn babies.

If there again arises a threat of a diphtheria epidemic in our country we wish to propose the following mode of action: Active immunization of all children at birth as well as at 6 months of age. This line of action ought to give a fairly good protection also for at least some years of preschool age.

If there arise many cases of diphtheria also in the first months of life we would propose to combine the active immunization mentioned above with passive immunization by vaccinating Schick positive mothers. It is not to be disregarded that in this case the active immunization at birth in many children will be without immunizing effect. The possibility nevertheless remains that it may, at least in some cases, have a sensitizing action (Downie et al., 1938) so that the six month injection will act as a booster dose. In large scale vaccination it is impossible to perform antitoxin titration or repeated Schick tests in order to settle the best mode of action in each single case. •

Summary.

In many countries nowadays the antitoxic immunity against diphtheria is most unsatisfactory. In Sweden less than 10 per cent of the non immunized adults have antibodies in «protective» concentrations. As a consequence the mothers but infrequently transfer to their offspring the passive immunity, which was formerly assumed to be the rule. Hence the question of immunization

already at an early age becomes topic. Earlier authors almost unanimously expressed the view that an immunization during the first months of life is not practicable the infants at this age being considered to have a poor antitoxin producing power. The results of the experiments published in this paper clearly demonstrate that this opinion is erroneous. Even the newborns react upon diphtheria immunization with aluminium precipitated toxoid, although the response in antibody formation is often delayed. Earlier workers seem to have been misled by one or several of the following errors: the slow reaction of the newborns; the more or less complete interference of «passive» antibodies, exceeding 1/50—1/10 A. U./cc, with the active immunization; and the importance of even minute amounts of «active» antibodies, indicating former sensitization, for the results of immunization.

Résumé.

De nos jours l'immunité antitoxique contre la diphtérie est fort peu satisfaisante dans bien des pays. En Suède moins de 10 % des adultes non-immunisés possèdent des antigènes en concentration «défensive.» Il en résulte que les mères ne transfèrent que rarement à leurs rejetons l'immunité passive qui était considérée de règle auparavant. Pour cette raison la question d'immunisation à une jeune âge est devenue actuelle. Des auteurs antérieurs expriment presque unanimement l'avis qu'une immunisation des enfants pendant les premiers mois de leur vie n'est pas faisable cet âge étant considéré n'avoir qu'une faible force productive d'antitoxine. Cependant, les résultats des expériences publiés dans ce journal prouvent distinctement que cette opinion est erronée. Même les nouveaux-nés réagissent à l'immunisation contre la diphtérie par du toxoïde précipité par l'aluminium, quoique le résultat en formation de substances antitoxiques soit souvent retardé. Des auteurs antérieurs paraissent avoir été égarés par une ou plusieurs des erreurs suivantes: la réaction tardive chez les nouveaux-nés, l'intervention plus ou moins complète de substances antitoxiques passives dépassant 1/50—1/10 A. U./cc en cas d'immunisation active, et l'importance de quantités même extrêmement petites d'antigènes «actives,» indiquant sensibilité antérieure, pour les résultats de l'immunisation.

Zusammenfassung.

Da die antitoxische Immunität gegen Diphtherie heutzutage in vielen Ländern unbefriedigend ist (in Schweden besitzen weniger als 10 % der nicht immunisierten Erwachsenen Antikörper in wirksamer Konzentration) und infolgedessen nur selten Mütter passive Immunität auf ihre Kinder übertragen, ist die Frage der Immunisierung im frühen Alter aktuell geworden. Die Ansicht, dass Immunisieren in den ersten Lebensmonaten wegen geringer Antitoxinproduktion untunlich sei, wird widerlegt. Selbst Neugeborene reagieren auf Diphtherie-Immunisierung mit durch Aluminium praecipitiertem Toxoid; frühere Autoren scheinen durch die langsame Reaktion der Neugeborenen, den hemmenden Einfluss von passiven Antikörpern bei aktiver Immunisierung und die Bedeutung selbst ganz geringer Mengen aktiver Antikörper irreführt worden zu sein.

Resumen.

En muchos países es hoy día muy poco satisfactoria la inmunidad antitóxica contra la difteria. En Suecia menos del 10 % de los adultos no inmunizados tienen anticuerpos en concentraciones «protectoras». Las madres, por consiguiente, sólo muy raras veces traspasan al descendiente la inmunidad pasiva que antiguamente se había considerado una regla general. De aquí que la inmunización, ya poco tiempo después del nacimiento, resulta tópica. Los autores anteriores habían creído siempre que la inmunización no es practicable durante los primeros meses de la vida, por considerar que a esta edad los niños no son suficientemente fuertes para producir antitoxina. Los resultados de los experimentos a que se refiere el presente artículo demuestran claramente la falsedad de esta opinión. Incluso los recién nacidos reaccionan ante inmunización contra difteria mediante toxoide precipitado de aluminio, aunque la formación de anticuerpos aparece muchas veces con retraso. Parece que los operadores anteriores habían sido desorientados por uno o varios de los errores siguientes: lenta reacción en los recién nacidos; injerencia más o menos completa de anticuerpos «pasivos», con una excedencia de 1/50—1/10 A. U./cc, con inmunización activa, además de la im-

portancia de incluso pequeñas cantidades de anticuerpos «activos», indicando sensibilización anterior, para los resultados de inmunización.

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Studies on Diphtheria.

III. The duration of immunity against diphtheria following vaccination as compared with that following clinical disease and carrier state.

By

BO VAHLQUIST and GUNNAR HACKZELL.

Diphtheria does not, as a rule, give life long immunity. Relapses of the disease with longer or shorter intervals are often observed. Sometimes the disease has been known to attack one and the same person three or four times or even more.

As far as we know the various types of diphtheria bacilli (*gravis*, *intermedius*, *mitis*, the different antigenic types of Tarnowsky) are from an immunological point of view uniform. Thus reinfections cannot be explained simply by change of bacillus type. They arise from an impaired immunological condition.

It is logical to assume that the immunity achieved after infection varies individually. In fact that must be a general rule. But for certain diseases, especially of virus origin such as measles, chicken pox etc., even faint reactions are sufficient to warrant life long immunity. In other instances, such as diphtheria, the individual variations become conspicuous.

It can hardly be doubted that the power of antibody formation shows marked individual variations. How may one otherwise explain that the effect of immunization, where the same dose of antigen is administered, varies materially as judged from the antibody concentration. Subjects with several relapses of diphtheria are in all likelihood minus variants in this respect. It must be borne in mind, however, that mild infections with low antigenic effect might contribute to the poor immunity result.

Table 1.

Antitoxin values in young women immunized two years (1.0 cm³ precip. toxoid) and one year (0.5 cm³ precip. toxoid) before the titration.

| PATIENT | AU / CM ³ | PATIENT | AU / CM ³ | PATIENT | AU / CM ³ |
|---------|----------------------|---------|----------------------|---------|----------------------|
| B-T | < 2,0 > 1,0 | L-N | < 0,80 > 0,40 | L-M | < 0,10 > 0,05 |
| N-N | < 2,0 > 1,0 | U-M | < 0,40 > 0,20 | Å-M | < 0,10 > 0,05 |
| U-U | < 0,80 > 0,40 | J-K | < 0,40 > 0,20 | W-N | < 0,10 > 0,05 |
| Z-E | < 0,80 > 0,40 | R-G | < 0,40 > 0,20 | B-F | < 0,10 > 0,05 |
| I-N | < 0,80 > 0,40 | R-P | < 0,40 > 0,20 | L-G | < 0,10 > 0,05 |

MEDIAN 0,30 (< 0,40 > 0,20) AU/CM³

This work is a study on the duration of immunity against diphtheria following vaccination as compared with that following clinical diphtheria and carrier state.

Technique. Antitoxin determinations according to the method of Claus Jensen (1933).

Material.

A. Vaccination group. This group comprises fifteen young women aged 18—19 years, all pupils at a highschool for girls at Uppsala. They were immunized for the first time in April 1944 with a single dose of 1.0 cc. vaccine. (Aluminium precipitated toxoid, 45 flocculation units per cc. Preparation according to Ericsson (1946); for the second time in March 1945 with a single dose of 0.5 cc. vaccine. The antitoxin determinations were performed in March 1946 (Table 1). Simultaneous throat and nose swabs on Clauberg substrate gave no growth of *Corynebact. diphtheriae*.

B. Clinical diphtheria group. All patients in this group and the group C belonged to the material of the City Hospital for Contagious Diseases in Stockholm. Two sub-groups were selected.

One of these consisted of patients, who had been treated in the hospital during the period Jan. 1st 1944 until April 1st 1945. As the analyses were made in the spring of 1946 this means an interval between disease and follow-up of one to two years. The

Table 2.

Antitoxin values in patients previously treated for diphtheria.

Between one and two years previously.

| PATIENT | SEX | AGE AT ONSET (YEARS) | DIAGNOSIS ¹⁾ | TYPE OF BACILLI ²⁾ | SERUM TREATMENT | | STAY IN THE HOSPITAL (DAYS) | INTERVAL BETWEEN DISEASE AND TITRATION (MONTHS) | AU/CM ³ |
|---------|-----|-------------------------|-------------------------|-------------------------------|------------------------------|----------------|--------------------------------|--|-----------------------|
| | | | | | DAYS AFTER ON-SET OF DISEASE | DOSAGE (UNITS) | | | |
| E-N | ♂ | 9 | D. FAUC. I | MITIS + | 3 | 6,000 | 73 | 16 | -2.0 |
| E-D | ♂ | 4 | D. FAUC. II | GRAVIS + | 3 | 9,000 | 166 | 20 | < 0.40 > 0.20 |
| E-N | ♀ | 12 | D. FAUC. I | MITIS + | — | 0 | 89 | 16 | < 0.40 > 0.20 |
| E-N | ♀ | 6 | D. FAUC. I | GRAVIS | 1 | 18,000 | 47 | 26 | -0.20 |
| E-T | ♂ | 11 | D. FAUC. II TBC | — | 3 | 0 | 90 | 25 | < 0.20 > 0.10 |
| E-N | ♂ | 21 | D. FAUC. II | MITIS + | 2 | 15,500 | 87 | 24 | < 0.10 > 0.05 |
| E-G | ♂ | 10 | D. FAUC. I | MITIS + | — | 0 | — | 18 | < 0.10 > 0.05 |
| E-D | ♀ | 18 | D. FAUC. I-II | — | — | 0 | 11 | 22 | < 0.10 > 0.05 |
| E-N | ♂ | 17 | D. FAUC. III-IV | GRAVIS | 3 | 186,000 | 63 | 16 | -0.05 |
| E-N | ♀ | 17 | D. FAUC. II | MITIS + | 3 | 27,000 | 83 | 14 | < 0.02 > 0.01 |
| E-C | ♀ | 19 | D. FAUC. II | INTERMED | 5 | 18,000 | 42 | 15 | < 0.02 > 0.01 |
| E-T | ♂ | 5 | D. FAUC. I TBC | — + | — | 0 | 83 | 25 | < 0.02 > 0.01 |
| E-N | ♀ | 12 | D. FAUC. IV | MITIS + | 5 | 40,000 | 136 | 16 | < 0.005 > 0.001 |
| E-T | ♀ | 11 | D. FAUC. II | MITIS + | 3 | 9,000 | 39 | 17 | -0.002 |
| E-T | ♂ | 6 | — | — | — | 0 | 19 | 18 | < 0.0005 |
| E-C | ♂ | 18 | D. FAUC. II | GRAVIS | 5 | 18,000 | 41 | 17 | < 0.0005 |
| Median | | 12 | D. FAUC. II | | 3 | 9,000 | 63 | 18 | 0.075 (< 0.10 > 0.05) |

¹⁾ I = Scattered patches on tonsils. Patient unaffected.

II = Membranes covering both tonsils. Patient unaffected

III = Membranes reaching beyond tonsils. Patient slightly affected.

IV = Membranes reaching beyond tonsils. Patient intoxicated.

²⁾ + Denotes that the toxicity of the bacilli has been proved in animal experiment.

patients in the other sub-group had been treated during the period Jan. 1st 1925 until Febr. 1st 1926, the interval therefore being about twenty years. In each case the record was checked as to the typical clinical picture and the presence of *C. diphtheriae*. The data concerning the bacterial findings are, of course, not as reliable in the earlier group as in the later one. None of the subjects investigated had had a relapse. Those patients, who had been vaccinated during the vaccination campaign of recent years, were, of course, excluded. Otherwise no selection was made. On the average the cases of 1925—26 were slightly more serious than those of 1944—45. The age of the subjects investigated was at

Table 3.

Antitoxin values in patients previously treated for diphtheria.

Interval between disease and titration 20 years.

| PATIENT | SEX | AGE AT ONSET (YEARS) | DIAGNOSIS ¹⁾ | SERUM TREATMENT | | STAY IN HOSPITAL (DAYS) | INTERVAL BET- WEEN DISEASE AND TITRATION (YEARS) | AU/CM ³ |
|---------|-----|----------------------------|-------------------------|----------------------------------|-------------------|----------------------------------|---|-----------------------|
| | | | | DAYS AFTER ON- SET OF DISEASE | DOSAGE (UNITS) | | | |
| A-N | ♀ | 6 | D FAUC I | — | 0 | 21 | 20 | < 0.20 > 1.10 |
| N-M | ♂ | 6 | D FAUC III | 2 | 18,000 | 33 | 20 | < 0.10 > 0.05 |
| K-K | ♂ | 9 | D FAUC I | — | 0 | 25 | 20 | < 0.10 > 0.05 |
| N-R | ♂ | 7 | D FAUC III | — | 54,000 | 67 | 20 | < 0.05 > 0.02 |
| J-N | ♂ | 11 | D NAS I | — | 0 | 34 | 20 | < 0.02 > 0.01 |
| K-N | ♂ | 5 | D FAUC III | 12 | 72,000 | 30 | 20 | < 0.01 > 0.005 |
| O-N | ♂ | 15 | D FAUC IV | 6 | 108,000 | 100 | 20 | < 0.005 |
| H-M | ♀ | 12 | D FAUC III-IV | 1 | 49,500 | 55 | 20 | < 0.002 > 0.001 |
| L-M | ♂ | 10 | D FAUC IV | 4 | 63,000 | 59 | 20 | < 0.001 > 0.0005 |
| L-E | ♂ | 6 | D FAUC IV | 1 | 128,000 | 101 | 20 | < 0.001 > 0.0005 |
| E-M | ♀ | 5 | D FAUC II | 3 | 9,000 | 36 | 20 | < 0.0005 |
| K-N | ♂ | 9 | D FAUC III-IV | 1 | 99,000 | 64 | 20 | < 0.0005 |
| H-N | ♀ | 9 | D FAUC IV + D NAS I | 3 | 180,000 | 48 | 20 | < 0.0005 |
| O-G | ♂ | 8 | D FAUC II | 4 | 21,000 | 19 | 20 | < 0.0005 |
| N-N | ♂ | 11 | D FAUC III | 4 | 18,000 | 15 | 20 | < 0.0005 |
| MEDIAN | | 9 | D FAUC III | 3 | 49,500 | 34 | 20 | 0.005 < 0.002 > 0.001 |

¹⁾ I = Scattered patches on tonsils. Patient unaffected.

II = Membranes covering both tonsils. Patient unaffected.

III = Membranes reaching beyond tonsils. Patient slightly affected.

IV = Membranes reaching beyond tonsils. Patient intoxicated.

the time of the antibody determination in the former group between 36 and 26 years, in the latter between 23 and 6 years. Other inherent data are found in the tables 2 and 3.

C. *Carrier group.* These subjects were selected in the same manner as the foregoing group. Every case had demonstrated at least two positive cultures, most of them had long series of positive findings. If the record indicated transient manifest disease before entrance to the hospital the case was not accepted though the diagnosis registered was «carrier». Yet single cases included in the material had a history of transient faint choryza or slight rise of temperature for a day or two. The possibility can therefore not

Table 4.

Antitoxin values in patients previously treated as carriers of diphtheria bacilli.

Interval between carrier state and titration 1—2 years.

| PATIENT | SEX | AGE AT CARRIER PERIOD (YEARS) | TYPE OF BACILLI ¹⁾ | TREATMENT | MINIMAL LENGTH OF CARRIER STATE (DAYS) | INTERVAL BETWEEN CARRIER STATE AND TITRATION (MONTHS) | AU / CM ⁵ |
|---------|-----|-------------------------------|-------------------------------|---------------|--|---|---------------------------|
| E-T | ♀ | 32 | MITIS | TONSILLECTOMY | 2 | 27 | <1.60 >0.80 |
| R-D | ♀ | 4 | MITIS | | 21 | 12 | <1.60 >0.80 |
| H-N | ♀ | 35 | — | | 3 | 21 | <0.40 >0.20 |
| E-M | ♀ | 7 | MITIS + | | 21 | 20 | <0.40 >0.20 |
| K-N | ♀ | 20 | GRAVIS | | 33 | 22 | <0.20 >0.10 |
| E-M | ♀ | 9 | INTERMED. | | 41 | 20 | <0.10 >0.05 |
| L-T | ♀ | 11 | — + | | 130 | 23 | <0.10 >0.05 |
| E-D | ♂ | 19 | MITIS | | 9 | 17 | <0.05 >0.02 ²⁾ |
| J-N | ♂ | 8 | INTERMED. | | 32 | 22 | <0.05 >0.02 ²⁾ |
| N-G | ♂ | 6 | GRAVIS + | | 127 | 25 | <0.005 >0.003 |
| G-R | ♀ | 5 | GRAVIS | TONSILLECTOMY | 7 | 19 | <0.005 >0.0005 |
| B-K | ♂ | 8 | — + | | 66 | 22 | <0.0005 |
| MEDIAN | | 9 | | | 26 | 22 | 0.055 (<0.10 >0.05) |

¹⁾ + Denotes that the toxicity of the bacilli has been proved in animal experiment.

²⁾ Sore throat during one day before admittance to the hospital.

be excluded that the true carriers are mixed up with a few cases of carrier state after a recent mild form of manifest disease. The age of the subjects investigated was at the time of the titration between 49 and 22 years in the age group 1925—1926 and between 37 and 5 years in the age group 1944—45. Other inherent data are found in the tables 4 and 5.

Results. These are collected in the tables 1 to 5 and might be summarized as follows (table 6).

A. Vaccination group. The fifteen young women, who were immunized with 1.0 cc. of vaccine two years before and with 0.5 cc. of vaccine one year before, were remarkably uniform with respect to their antibody concentration. All of them were well

Table 5.

Antitoxin values in patients previously treated as carriers of diphtheria bacilli.

Interval between carrier state and titration 20 years.

| PATIENT | SEX | AGE AT CARRIER PERIOD (YEARS) | TREATMENT | MINIMAL LENGTH OF CARRIER STATE (DAYS) | INTERVAL BETWEEN CARRIER STATE AND TITRATION (YEARS) | AU / CM ³ |
|---------|-----|-------------------------------|-----------------|--|--|----------------------|
| L - N | ♀ | 27 | — | 46 | 20 | <0.10 > 0.05 |
| E - N | ♂ | 1½ | — | 82 | 20 | <0.10 > 0.05 |
| B - M | ♀ | 9 | — | 142 | 21 | <0.10 > 0.05 |
| P - N | ♂ | 5 | — | 109 | 20 | = 0.05 |
| L - M | ♀ | 1¾ | — | 94 | 20 | <0.05 > 0.02 |
| C - N | ♀ | 36 | — | 50 | 21 | <0.05 > 0.02 |
| A - N | ♂ | 1½ | — | 45 | 21 | <0.01 > 0.005 |
| H - N | ♂ | 11 | — | 4 | 20 | <0.003 > 0.001 |
| C - A | ♂ | 4 | — | 13 | 21 | <0.0005 |
| W - E | ♀ | 7½ | SERUM, 6.000 U | 4 | 21 | <0.0005 |
| S - N | ♀ | 4 | — | 10 | 20 | <0.0005 |
| L - N | ♂ | 7½ | SERUM, 1.500 U. | 9 | 20 | <0.0005 |
| MEDIAN | | 4 | | 45 | 20 | 0.015 (<0.02 > 0.01) |

above the «immunity level» with minimum values of 0.05 A. U./cc., the maximum value observed was <2.0 > 1.0 A. U. The median value is calculated to 0.30 A. U./cc.

B. Clinical cases group. It is obvious that the antibody values of the group 1925—26 are inferior to those of 1944—45, as the diphtheria frequency and hence the possibility of repeated infection had been low in the meantime. Five out of sixteen cases in the group 1925—26 had no measurable antibodies in their blood (<0.0005 A. U./cc.) and four further cases were below «immunity level» (<0.02 A. U./cc.). Only one case had a relatively high antibody content, <1.6 > 0.80 A. U./cc. The median value is as low as 0.0015 A. U./cc.

In the group 1944—45 two of the cases, tested 17 and 18 months after their disease, lacked antibodies completely. Another five cases were below immunity level, whereas nine other cases

Table 6.

Comparison of the antitoxin values of different groups: vaccinated subjects, former carriers, former clinical cases of diphtheria and controls.

| GROUP | TABLE | NUMBER OF CASES IN ALL | NUMBER OF CASES IN EACH OF THREE TITER CLASSES | | | MAXIMAL VALUE OF THE GROUP | MEDIAN VALUE OF THE GROUP |
|-------------|----------------|------------------------|--|------------------------|----------------------|----------------------------|---------------------------|
| | | | < 0,0005 | $\bar{\approx}$ 0,0005 | $\bar{\approx}$ 0,02 | | |
| VACCINATED | 1 | 15 | 0 | 0 | 15 | < 2,0 > 1,0 | 0,30 |
| CARRIERS | 4 | 12 | 1 | 2 | 9 | < 1,60 > 0,80 | 0,075 |
| CLIN. CASES | 2 | 16 | 2 | 5 | 9 | = 2,0 | 0,075 |
| CARRIERS | 5 | 12 | 4 | 2 | 6 | < 0,10 > 0,05 | 0,015 |
| CLIN. CASES | 3 | 15 | 5 | 6 | 4 | < 0,20 > 0,10 | 0,0015 |
| CONTROLS | 4 ¹ | 85 | 62 | 17 | 6 | (< 20 > 10) | < 0,0005 |

¹) From table 3, part I of this series of papers (VAHLQUIST, 1948).

were well above this level with a maximum value of <2.0>1.0 A. U./cc. The median value of this group is 0.075 A. U./cc.

The figures do not indicate any correlation between the gravity of the former disease and the actual antibody concentration. The limited material does not imply that the antitoxin formation has been strongly impaired by the serum treatment. A fact which is somewhat surprising.

C. *Carrier group.* In the group of 1925—26 five out of sixteen patients investigated were completely without antibodies. Further five were below the immunity level (<0.02 A. U./cc.). The maximum value among the remaining six cases was <0.80>0.40 A. U./cc. The median value calculated 0.0075 A. U./cc.

For the group 1944—45 the corresponding figures were one, four and nine subjects respectively, the maximum value observed <1.6>0.80 A. U./cc. and the median value 0.20 A. U./cc.

Discussion. We believe that we are justified in drawing the following conclusions from the results given above.

1. The antibody formation after vaccination according to the method adopted (1.0 and 0.5 cc of aluminium precipitated toxoid with one year interval) is probably more potent and anyway

of longer duration than that achieved after clinical disease or carrier state.

2. The difference may be explained as a consequence of dissimilarities in the amount of antigen at work (toxoid or toxin) or/and in the mode of reaction to the antigen stimulus.

As a matter of fact the quantity of antigen present in the diphtheria vaccine is very large. The Swedish vaccine used contains in the form of toxoid a quantity of antigen corresponding to about 1500 minimal lethal doses per cc. It might be expected, perhaps, that the toxin formation in cases of diphtheria is considerable too. Observations in accidents, where undiluted diphtheria toxin has been injected in connection with Schick testing do not give support to such a view, however. Skoog (1944) observed not only local necrosis but also signs of severe diphtheria neuritis and suspected myocardial disease following the intracutaneous injection of 10 minimal lethal doses. In this connection a result of Zoelsch (1933) is of interest. In several patients who were in complete lack of antitoxin even after a relapse of diphtheria he succeeded in producing an antitoxin titer by vaccination.

It has been observed by earlier investigators that some patients with diphtheria show an antibody response which is faint and rapidly subsiding (Madsen 1939 and others). According to the prevalent opinion this fact implies that the diphtheria disease is especially liable to attack subjects with a constitutionally founded faint reactive power. This ought particularly to be the case, when there is question of relapses.

Our results make clear that some individuals have indeed lost their antibodies completely, if ever they had any, already after the lapse of about one year and a half (exactly 17 and 18 months). As might be expected the number of such cases is greater after the lapse of twenty years, five out of sixteen.

Which is the correct interpretation of our results? Do they support the view that the diphtheric disease attacks especially individuals with a poor antitoxin producing ability? To elucidate this problem an analysis of the situation in former carriers was performed. The results given above from this investigation show that the antibody situation is much the same in the carriers. The

mean values are somewhat higher in this group but the differences are not very striking and in both groups we find a number of individuals with low antibody concentration or with no antibodies at all.

These results hardly support the view of an over representation of poor reactors among the clinical cases of diphtheria. It might be of course that the amounts of antigenic substance are lower in the clinical cases wherefore the differences should have been more marked provided the antigen effect had been identical. But this is an unproved fact. For the time being it must be noted as remarkable that the difference with respect to the antibody concentration between former clinical cases and carriers is so slight.

Summary.

A comparison is made between the antitoxin values found in the following groups of subjects: I. Subjects vaccinated two years and one year ago; II and III. Cases of clinical diphtheria 2 and 20 years ago; IV and V. Diphtheria carriers 2 and 20 years ago and VI. Non-immunized control subjects. The results are condensed in table 6. The following facts should be stressed: The vaccinated subjects are by far better off, as judged from the antitoxin concentration, than the former clinical cases or carriers. The former carriers have on the whole somewhat better antitoxin values than the former clinical cases, when examined after 2 and 20 years but the difference is not very striking.

The results do not give support to the view often held, namely, that the diphtheria cases represent a selection of poor reactors.

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Résumé.

Une comparaison est faite entre les valeurs d'antitoxine trouvées chez les groupes d'individus suivants: I. Des sujets vaccinés il y a deux ans et il y a un an; II. et III. Des cas de diphtérie clinique d'il y a deux ans et d'il y a 20 ans; IV, et V. Des porteurs de diphtérie d'il y a deux ans et d'il y a 20 ans; VI. Des sujets de contrôle

non-immunisés. Les résultats sont indiqués dans le tableau 6. Les faits suivants méritent d'être accentués: Du point de vue de la concentration d'antitoxine les sujets vaccinés se trouvent dans une position plus favorable que les cas cliniques antérieurs ou les porteurs de diphtérie. Les anciens porteurs ont en général des valeurs d'antitoxine un peu meilleures que les anciens cas cliniques, quand on les examine 2 et 20 ans plus tard, mais la différence n'est pas frappante.

Les résultats ne donnent pas d'appui à l'opinion souvent exprimée que les cas de diphtérie représentent une sélection de réagissants faibles.

Zusammenfassung.

Vergleich der Antitoxin-Werte folgender Gruppen: 1. vor 2 resp. 2 Jahren geimpfte Personen; 2. und 3. vor 2 resp. 20 Jahren gewesene klinische Fälle; 4. und 5. vor 2 resp. 20 Jahren gewesene Bazillenträger; 6. nicht immunisierte Kontrollpersonen. Die Geimpften zeigen viel höhere Antitoxin-konzentration als die klinischen Fälle oder Bazillenträger. Die gewesenen Träger haben etwas bessere Werte als die früheren klinischen Fälle. Die Meinung, dass die Diphtheriefälle schwache Reaktion aufweisen, wird durch diese Untersuchungen nicht bestätigt.

Resumen.

En este artículo se hace una comparación entre los valores de antitoxina encontrados en los siguientes grupos de individuos: I: Individuos vacunados uno o dos años antes. II y III: Casos de difteria clínica hace 2 y 20 años. IV y V: Portadores de difteria hace 2 y 20 años. Y VI: Individuos controlados que no han sido inmunizados. El cuadro 6 muestra un resumen de los resultados obtenidos. Se debe hacer especial mención de los siguientes hechos: Los individuos vacunados están en condiciones mucho mejores, estimando la concentración de antitoxina, que los anteriores casos clínicos o portadores. Los portadores antiguos tienen en general mejores valores de antitoxina que los antiguos casos clínicos al haber sido examinados después de 2 y 20 años, pero la diferencia no llama la atención.

Los resultados no apoyan el punto de vista muchas veces defendido de que los casos de difteria representan una selección de reactores pobres.

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Renal Thrombosis with Infarction in the Newborn. Two Different Forms.

By

PH. SANDBLOM.

Infarction of one or both kidneys in association with renal venous thrombosis is not uncommon in infants. In a necropsy material of 800 newborns Cruikshank (4) found thirty cases of visceral thrombosis; fifteen out of these were renal venous thromboses. The condition occurs especially often in acute infections with dehydration, such as gastro-enteritis. Barenberg et al (2) in a material of 25 newborns which had died in an epidemic of gastro-enteritis found five renal venous thromboses with infarction.

This subject has mainly been studied by the pathologists — evidently due to the fact that the condition but rarely is diagnosed ante-mortem. The symptoms are often vague (Barenberg (2), Morison (6)) and are therefore screened behind the primary disease. It is remarkable that the urine often is normal or nearly normal (2, 6).

The renal infarction is probably often the terminal cause in these children. The question arises as to whether a number of them might be saved if the disease were diagnosed more frequently. The author will further consider this possibility in connection with a case which in this Hospital recently was treated with a favourable outcome.

K. L. V. Med. 255/47. Surg. 483/47. Female, 5 days of age, healthy parents, full term delivery 2/28 1947. Weight 3 600 g. Forceps delivery because of feeble labour pains during 48 hours. The infant was not cyanotic after parturition. 2.5 g vitamin K was administered the

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same day. Prothrombin value five days later 87. During the first days of life the infant seemed well and fed well. On the fifth day of life the child suddenly became ill, pale, and showed abdominal distension. It was referred to the Medical ward of the Children's Hospital with the suspicion of abdominal hemorrhage.

Examination: Normally developed infant, general condition somewhat deteriorated. Skin rather pale and slightly jaundiced. Temperature normal. No cyanosis, dyspnea or edema. Abdomen rather tense and distended. At the site of the right kidney a firm mass, twice the size of a child's fist, is palpated.

X-ray examination showed a solid mass in the right section of the abdominal cavity, «probably a renal tumor».

Laboratory findings: Blood: Hgl 105 per cent. Red cell count 4 800 000. White cell count 26 800 of normal composition. Thrombocytes 204 000. Mother and child blood group O Rh (+) · NPN 70 mg per cent. Urine: Albuminuria +. 3 mm bloody sediment. Feces: normal.

During the following 24 hours the patients's condition deteriorated and the urine was macroscopically bloody. The child was considered to have a congenital renal tumor with a hemorrhage in progress. The condition of shock was considered to be due to necrosis of the tumor. Immediate operation seemed imperative in order to save the child and further urologic studies had to be abandoned.

Operation (S-m) was performed transperitoneally in order to give a view of the renal hilus and also to afford information as to the condition of the other kidney.

Left-sided nephrectomy. Right paramedian rectus sheath incision, appr. 6 cm long at the umbilical level, there after a T-shaped transverse incision at the umbilical level, appr. 5 cm long, towards the flank. A small amount of free blood is found in the abdomen. Behind peritoneum a bluish-red mass bulges forth on the right side. The parietal peritoneum is opened over the mass, which fairly easily is isolated. It is seen to consist of the right kidney. The ureter is divided. Hilus is handled very gently in order to avoid lesion to the vessels. These are divided individually. The artery is narrow and normal. The renal vein is enlarged and obviously thrombosed. The clot is palpated in vena cava up to the posterior side of the liver. The left renal vein is free, but emerges at the site where the thrombus already fills the greater portion of vena cava. As it is seen that there is no possibility of removing the thrombus, one must remain content with dividing the renal vein and removing the kidney. Scrupulous hemostasis. Suture in layers. The parietal peritoneum over the tumor can not be closed due to the size of the defect.

At section an entirely injected adipose capsule is found with a lobulated kidney, twice the normal size, blackish-red in color.

The borderline between medulla and cortex may be distinguished, however. No tumor is observed. There is probably a total infarction of the kidney. Post-operative transfusion, 50 ml of whole blood of group O Rh + is given without complications.

Pathological-anatomical examination, by Professor Bergstrand, showed complete hemorrhagic infarction of the kidney. A number of the veins of the renal hilus were filled with thrombus masses. A number of grains of calcium were found in these. There was no pyelo-nephritis.

The patient supported the operation well. The urine became normal after a week and the patient then began to gain weight.

Nonprotein nitrogen normal after 2 weeks. There was some apprehension as to whether the thrombosis would progress to the right kidney, but there were no symptoms suggesting this.

At examination 4 months after the intervention the patient appeared to be perfectly healthy.

Summary: A previously healthy female infant which has had a difficult forceps delivery is on the fifth day of life taken ill with shock, abdominal distension, a mass at the site of the right kidney, and macroscopic hematuria. Nephrectomy is carried out, on vital indication and on the suspicion of hemorrhage from a right-sided renal tumor. A total renal infarction is found, as well as a thrombus, reaching from the renal vein up into vena cava. The patient made a rapid recovery.

Commentary.

The presence of calcium in the thrombi of the renal hilus indicates that these were not recent. It seems possible that they were brought about by trauma during the difficult delivery. There was no other etiologic factor in the form of disease in the mother or infection, dehydration, or blood changes in the child.

The sudden onset of symptoms on the fifth day of life justifies the assumption that the thrombus then occluded the main branch of the renal vein, suddenly producing a total infarction with symptoms of renal swelling, shock and hematuria. The picture is in this case clear, not being blurred by the symptoms of a primary infection.

I have in the literature not found more than two instances of infants with a total renal infarction being operated with a favourable outcome (Campbell (3)).

The present case shows great similarity with these. They also had a sudden onset without previous infection or dehydration, with symptoms of shock and palpable mass at the site of the right kidney. One of the cases showed microscopic hematuria, the other case had a massive macroscopic hematuria. None of these cases had been subjected to birth trauma and the etiology is in these cases entirely obscure; certain blood changes: in the first case an abnormally short coagulation- and bleeding-time, in the second case a moderate polyglobulism can hardly be considered of importance. The kidney removed in Campbell's first case does not seem to have revealed signs of infection, while that of the second case was markedly inflamed; but as it was not removed until four weeks after the infarction occurred it is possible that the inflammation may have been secondary.

The picture is in these three cases very similar to that in adults described by Hepler (5) as follows: «The clinical picture is definite and consists in the sudden onset of hematuria, lumbar pain, and enlargement of the kidney». (8 operated cases, of which 6 survived, are found in the literature.)

Hepler describes a characteristic case in a girl, two-and-one-half years old, where the thrombus primarily was formed in vena cava, subsequently progressing to one of the kidneys, with recognized and characteristic symptoms. Following removal of this kidney, however, the thrombosis progressed over to the other kidney, leading to death.

On the other hand these three cases show wide divergence from renal infarctions in infants, which arise secondarily to infections with dehydration. In these the course of the renal complication usually is without symptoms and with no or slight changes of the urine (Barenberg, Morison).

Oppenheim (8) on the basis of accurate microscopical studies considers that the renal venous thromboses are secondary to a hemorrhagic infarction. This again he considers due to a primary lesion of the capillary walls of the renal medulla. Morison

(6) found 4 cases of infarction without thrombosis in his material of 18 cases (he on the other hand also found 5 cases with thrombosis of the smaller renal veins without infarction).

Hepler (5) suggests a subdivision of cases of primary renal venous thrombosis into 3 groups:

- 1) those arising in the capillaries and the smallest veins, progressing to the larger vessels.
- 2) those primarily arising in the main branch and progressing peripherally.
- 3) those arising in the larger main branches and progressing in both directions.

Hepler reports that the type first mentioned is the usual in infants with enteritis.

Conclusion.

The comparison drawn justifies the assumption that renal infarction in children appears in two separate forms with different etiology and clinic.

1. A primary and evidently very rare form to which belong the present case as well as Campbell's 2 cases and possibly also Morison's (6) case 11. The etiology is obscure, it may possibly be due to birth trauma. The infarction appears soon after birth (5—7—5—7 days in the cases described above) in otherwise healthy children and gives alarming symptoms with shock, hematuria and renal enlargement. The thrombus probably arises in one of the larger renal veins and gives rise to a sudden disturbance of circulation on occluding the main branch.

These cases may be saved by nephrectomy and the prognosis is then good.

2. A secondary, fairly common form, in which infarction is secondary to infection with dehydration. This infarction occurs slowly and the symptoms are obscured by the primary disease. The thrombi are first formed in the radicle veins. No, or but very slight, changes in the urine. The diagnosis is difficult; it is but rarely made ante-mortem. This is probably immaterial, as an operative therapy probably would not save these infants, especially as the changes frequently are bilateral although in

different stages (Aschner 1, Hepler 5). (For further information regarding this group see Morison (6), Barenberg et al (2) and Oppenheim (8).)

Résumé.

L'infarcissement total du rein chez l'enfant se présente sous deux formes distinctes, chacune comportant une étiologie et des signes cliniques propres.

I. Une forme primitive, très rare, à laquelle appartiennent le cas rapporté dans ce travail, les deux cas de Campbell et peut-être le cas N° 11 de Morison. L'étiologie en est obscure, peut-être en rapport avec un traumatisme obstétrical. L'infarctus apparaît dès les premiers jours (5^e—7^e—5^e et 7^e jour dans les cas cités ci-dessus) chez des enfants par ailleurs en bonne santé et donne des signes alarmants avec choc, hématurie, augmentation de volume du rein. La thrombose se produit probablement dans une des veines les plus importantes et provoque une perturbation circulatoire subite par occlusion du tronc principal. Ces cas devraient être sauvés par la nephrectomie, avec un bon pronostic ultérieur.

II. Une forme secondaire, relativement commune, dans laquelle l'infarctus succède à une infection avec déshydratation. Cet infarctus se développe à bas bruit et les symptômes en sont masqués par l'affection causale. Les thrombus se forment d'abord dans les veinules. Pas, ou peu de modifications des urines. Le diagnostic est difficile; il n'est que rarement porté ante-mortem. Ce retard est probablement sans importance pratique, puisqu'une action chirurgicale ne sauverait sans doute pas ces enfants, atteints fréquemment de lésions bilatérales à diverses étapes.

Zusammenfassung.

Die totale Nieren-Infarzierung bei Kindern tritt in zwei nach Ätiologie und klinischen Erscheinungen ganz verschiedenen Formen auf.

1. Eine primäre, sehr seltene Form, zu welcher der hier berichtete Fall, die zwei Fälle von Campbell und vielleicht Fall Nr 11 von Morison gehören. Die Ätiologie ist unklar, steht möglicherweise mit einem Geburtstrauma in Zusammenhang. Der Infarkt

zeigt sich in den ersten Lebenstagen (bei den erwähnten Fällen am 5.—7.—5.—7. Tage) bei sonst ganz gesunden Kindern mit alarmierenden Erscheinungen, Shock, Hämaturie, Vergrößerung der Niere. Die Thrombose bildet sich wahrscheinlich in einer der grössten Nierenvenen und ruft durch Verschluss des Hauptastes eine plötzliche Zirkulationsstörung hervor. Diese Fälle können durch Nephrektomie gerettet werden mit günstiger Prognose.

2. Eine sekundäre Form, relativ häufig, bei welcher der Infarkt als Folge einer Infektion mit Dehydration auftritt. Dieser Infarkt entwickelt sich schleichend und die Symptome sind durch das Grundleiden verdeckt. Die Thromben bilden sich zuerst in den kleinen Venen. Keine oder nur geringe Veränderungen des Urines. Die Diagnose ist schwer und wird nur selten ante mortem gestellt. Das ist vielleicht praktisch belanglos, denn ohne Zweifel könnte ein chirurgischer Eingriff diese Kinder nicht retten, da die Veränderungen oft in verschiedenen Etappen beiderseits auftreten.

Conclusión.

La infartación renal en niños se presenta en dos distintas formas, con etiología y clínica distintas.

1. Una forma primaria y aparentemente muy rara, a la cual pertenecen tanto el presente caso como los dos de Campbell y posiblemente también el caso 11 (6) de Morison. La etiología es confusa, pero puede ser debida a trauma de nacimiento. La infartación aparece casi inmediatamente después del nacimiento (a los 5, 7, 5 y 7 días, respectivamente, en los susodichos casos) en niños por lo demás sanos y presenta síntomas alarmantes con choques, hematuria y agrandamiento renal. El trombo se origina probablemente en una de las venas renales mayores y produce repentinas alteraciones en la circulación ocluyendo la rama principal.

Estos casos pueden ser curados por medio de nefrectomía, después de lo cual el pronóstico es bueno.

2. Una forma secundaria bastante común en la cual la infartación es secundaria a la infección con deshidratación. La infartación se presenta con retardo y los síntomas están oscurecidos

por la primera enfermedad. Los trombos se forman primero en las venas de la radícula. No hay ninguna alteración o sólo una alteración muy insignificante de la orina. El diagnóstico es difícil; sólo raras veces se hace «ante mortem». Seguramente esto carece de importancia, ya que una terapia operatoria no salvaría probablemente a estos niños, sobre todo si se tiene en cuenta que muchas veces las alteraciones son bilaterales, aunque en distintos estadios.

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CASE REPORTS

A Case of Congenital Choledochus Cyst.

By

S. URWITZ.

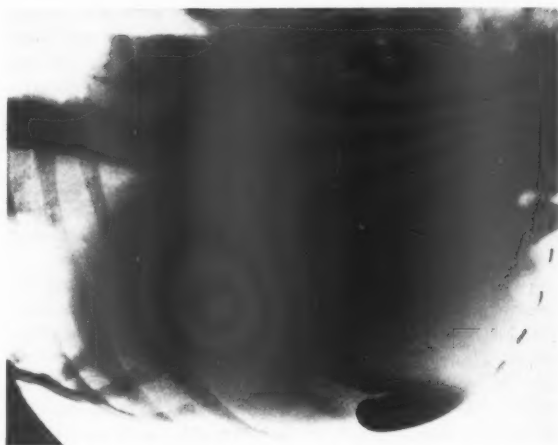
From the Samariten Children's Hospital, Stockholm.

Head: Professor NILS MALMBERG.

There are about 200 reports in the literature of congenital dilatation of the common bile duct, of which six are Swedish (2, 5, 8, 9, 12, 13). The malformation is nevertheless fairly little known, at the same time as it is exceedingly important, as surgical treatment at an early stage seems to give lasting recovery, and it has therefore been considered advisable to publish the following observations.

The patient, a boy, G. S., born on Dec. 10, 1939, was sent to the Samariten Children's Hospital by the school physician, suspected of having tumor of the abdomen. On admission, Dec. 14, the parents stated that the boy had not been ill or in pain. The tumor in question had been observed at the beginning of his first year at school, at the general physical examination. After a time, however, it was elicited that the boy had perhaps seemed a little tired during the past month. General condition good, weight 19.5 kg, no pain and no jaundice. Meulengracht icterus index, 1:6. In the right upper abdomen a painless, rather soft mass was palpated, which in the roentgenogram seemed to be connected with the liver, extending over the midline and out towards the flank. Four days later it could not be palpated. Apart from this vague finding from the abdomen and the fact that he was pale and appeared somewhat tired, nothing pathologic could be observed. The circumference of the abdomen varied between 53 and 55 cm, and the S. R. between 10 and 25 mm in 1 hour. Pyelographic examination after intravenous injection showed normal conditions. At an examination by cholecystography on Jan. 15 and March 17 no gallbladder shadow was visualized. Between the examinations he went to school and had no symptoms. A tentative diagnosis of dropsy of the gallbladder was made, and it was decided to perform an operation in the middle of April.

At the beginning of April, an angina tonsillaris, which was treated with sulfonamides, was complicated by an itching rash and severe jaundice with pale faeces. There were still no abdominal pains. He was admitted again, Apr. 21, and was then very fatigued, and had severe jaundice and several marks from scratching. Far to the right, in the abdomen, a mass having the characteristics of a cyst on palpation bulged out under



The cyst after injection of perabrodil, with the patient on his right side. The gallbladder looks like an appendix of the cyst.

the arch, and the upper part of the abdomen, on the right side, was entirely filled as far as to the left mammillary line by a firm, smooth, painless mass. Analysis of the urine showed abundant bile pigment. Puncture of the cystic mass with a very fine needle yielded a clear, greenish-yellow, foamy and mucous fluid containing staphylococci, which did not, however, show growth on cultivation. At roentgen examinations on various occasions the mass appeared to be of different sizes, and after injection of perabrodil a cyst, $9 \times 16 \times 14$ cm in size, was visualized. *Operation, May 5 (Johnson).* Cholecystostomy was done at the first operation. The normal-sized gallbladder was then seen to be extending into the cyst, from which 650 ml of fluid were drained, the final portion being very turbid. The boy's condition was so bad that the cyst was only stripped free at this operation. At the next stage, on May 7, a Witzel's operation was undertaken. The patient's condition, however, grew worse. The prothrombin index, which before the operation had been good except on one occasion, fell again, but was kept at a satisfactory level with vitamin K. Abdominal pain set in. He died on May 13, due to biliary peritonitis, which was verified at autopsy, a perforation the size of a pea with blood clots in the left posterior part of the cyst being observed. There was no evidence of defect in stomach or intestines and the contents of the stomach were not bilestreaked. Between the transverse colon and the lower part of the liver, to the right of the ligamentum falciforme he-

patitis, there was a cystic mass the size of a grapefruit filled with a thick, dark, bile-coloured, bloody fluid. A fine probe could easily be inserted into this mass through Vater's papilla. Signs of mechanical obstruction in connection with the papilla were not seen. On the superior anterior aspect of the cyst a passage the size of the little finger opened into the gallbladder, which was as large as a small pear and had a mucous membrane containing bile pigment but with no evidence of defect. From the superior posterior aspect of the mass opened two passages lying close to one another, one extending to the left lobe of the liver, the other to the right lobe. The mass had no obvious connection with the pancreas, which was of normal size with no evidence of defect. Grossly, the liver looked normal, and under the microscope it displayed clots of bile in several places and the periportal connective tissue was increased. The bile ducts and blood vessels showed no pathologic changes. The wall of the cystiform choledochus consisted of connective tissue, poor in cells, with fairly fine collagenic fibrils arranged in parallel lines. Muscle tissue and epithelium were lacking on the inner side of the wall. On the outside of the walls there were signs of recent hemorrhage and a slight accumulation of leukocytes. (Wahlgren.)

Many theories have naturally been advanced to explain this, in some cases, enormous cyst (cases are mentioned where more than 5 000 ml of fluid were obtained), especially as, in most instances, no obstacle to the drainage of the bile could be observed. The view now generally accepted is that it is an irregularity in the proliferation of the epithelial cells of the primitive, still homogeneous choledochus (15) that allows 1—2 cm of the choledochus nearest to Vater's papilla to assume normal size, while the rest continues to expand. Stenosis could never cause greater dilatation than the size of the small intestine. There are cases described from a premature infant weighing 1,890 gm (3) and also from a 1 month old girl (14).

Symptoms can begin at any age. In one report in 1943 (10), supplemented in 1946 (11), 3 cases between 60 and 70 years of age are mentioned. Seventysix per cent were not 25 years old and 77 per cent were women.

The syndrome of tumor, jaundice and pain point to the diagnosis, congenital choledochus cyst; the first two signs were reported in 77 and 70 per cent, respectively, and the third in 59 per cent in the report from 1943. The varying size and consistency of the mass may be regarded as very typical in early cases. The explanation lies perhaps in the fact that part of the wall of the cyst closes down like a valve at the spot where the dilated part of the duct passes over into the normal part. This part of the wall keeps the cyst closed until the pressure becomes great enough to open it, upon which some of the contents of the cyst are discharged into the intestine. When enough of the contents have been discharged to permit the wall of the cyst once again to fall across the opening of the

narrower part the cyst is closed up again. When the cyst reaches a certain size, a kink forms which causes bile stasis with jaundice and later, hemorrhagic diathesis. Roentgen examination of the bile passages after oral ingestion of a contrast medium shows no shadow, either because the contrast medium has become diluted too much where there is still no obstruction or because the passage is already completely closed.

When the condition is correctly diagnosed at an early stage the prognosis is fairly good; in one report, for instance, 4 patients recovered without after-effects out of 5 operated on (14). In the 1946 report there were only 12 out of 182 patients who showed a 4 year cure. In this report the mortality following operation was as high as 36 per cent, and in cases where the correct diagnosis had not been made, 62 per cent. There is only one form of treatment — operation as soon as possible, and most authors recommend choledochoduodenostomy in one operation. The risk of cholangitis has not proved to be as great as was previously feared. Roentgen examination carried out afterwards has proved that the contrast substance has passed into even the finest passages of the liver without any infection occurring (1).

Summary.

A report is made on a case of choledochus cyst. After injection of a contrast medium directly into the cyst a new type of roentgenogram pathognomonic for this condition was obtained. Owing to its size, the cyst could be punctured without undue risk and a roentgenogram was obtained showing the gall-bladder as an appendix to the cyst. Such an intervention ought to make it possible, in other cases also, to diagnose the condition at an early stage and submit the patient to operation in time.

Résumé.

On donne un compte-rendu d'un cas du kyste cholédocien. Après une injection directe dans le kyste d'une substance opaque on a obtenu un nouveau type de radiographie pathognomonique pour cet état. A cause de la grandeur du kyste on a pu faire la ponction sans risque et on a obtenu une radiographie montrant la vésicule biliaire comme un appendix du kyste. Une telle intervention devrait rendre possible, même dans d'autres cas, de faire de bonne heure un diagnostic de l'état et de soumettre à temps le patient à une opération.

Zusammenfassung.

Bei einem Fall einer Choledochus-Zyste erhielt man nach Injektion eines Kontrastmittels in die Zyste einen neuen Typ eines für diesen Zustand pathognomonischen Röntgenbildes. Wegen ihrer Grösse konnte die Zyste leicht punktiert werden und das Röntgenbild zeigte die Gallenblase gleichsam als Anhängsel der Zyste. Eine derartige Untersuchung dürfte auch in anderen Fällen eine frühzeitige Diagnose ermöglichen.

Resumen.

El presente artículo es una memoria sobre un caso de quiste colédoco. Después de una inyección de un medio de contraste aplicada directamente en el quiste, se obtuvo un nuevo tipo de roentgenograma patognomónico. A causa del tamaño el quiste pudo ser punzado sin peligro innecesario y se obtuvo un roentgenograma que mostraba la vesícula biliar como un apéndice del quiste. Una intervención de este género debe permitir un diagnóstico, también en otros casos, en los comienzos de una enfermedad y operar a tiempo al enfermo.

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A Case of Congenital Cystic Lung in a Child, just under 2 Years old, treated with Pneumonectomy.

By

SVEN BRECHLING.

Communication from the Department for Lung Surgery of the Øresundshospitalet, Copenhagen. Chief: Senior Surgeon TAGE KJÆR, M. D.

Though the number of successful pneumonectomies has been greatly increasing during the 15 years that have passed since NISSEN was able to publish the first case of a patient surviving this interference, com-

munications about infants are still few, in spite of the fact that no small proportion of the number of patients operated on is just represented by cases of congenital bronchiectasia. Apart from RIENHOFF's pneumonectomy of 1933 on a girl, aged $3\frac{1}{2}$ years, who had a sarcoma, and ROBERT's case of 1937, a 2-year-old boy with a congenital pulmonary cyst, both of which took a favourable course, the entire literature does not till now contain any communication about pneumonectomy on children below the age of 5 years or so.

As the Department for Lung Surgery of the Øresundshospitalet has had a case of a boy, just under 2 years old, who was successfully operated on and thus is the youngest patient altogether who has yet undergone this comparatively large interference with a good result, his case record is briefly reported in the following.

The patient was born at term after normal delivery in April 1944. He was breast-fed for nearly 6 months and was then given an ordinary infant's diet with an addition of vitamins. He was in completely good health until, at the age of 18 months, he developed symptoms of bronchitis with a high fever and cough, for which reason he was admitted to hospital. A few days after, however, he was transferred to the Department for Lung Surgery, as an X-raying had revealed multiple cysts in the left inferior lobe with infiltration in the lung and exudate in the pleura.

On admission to the Øresundshospitalet he was very exhausted, his skin being pale and cool. A trial puncture with evacuation of pus was made at once and during the next few days he was treated with chemotherapeutics, both by the mouth and with local application in the pleural cavity in connection with punctures. Already 3 days after his admission to this department, however, the daily thoracocenteses had to be given up, as the pus was too thick to pass out through the cannula, and a thin drainage tube was introduced, being connected with continuous suction. But as the secretion was rather increasing during the days that followed, a radical operation was decided on in order to remove the focus causing the great loss of proteins and thus slowly breaking down his physical resistance.

In January 1946, when the patient was 21 months old, a leftsided pneumonectomy was made after preceding prophylactic penicillin and sulfathiazole therapy. The following is recorded, *inter alia*, about the operation:

10 cm of the 7th rib were excised. Symphysis was ascertained, being loosened comparatively easily with the fingers. The entire inferior lobe almost occupied the thorax, being of consistence and appearance rather like a cystic kidney. One of the cysts was perforated and pus was evacuated from it. The superior lobe was completely atelectatic of appearance and, consequently, it was necessary to make pulmomectomy. It

was comparatively easy to isolate the entire lung, blunt instruments being used almost everywhere; the tourniquet, consisting on this occasion of thick silk, was applied. There was no bleeding when the lung was removed.

The patient was able to stand the interference amazingly well; the blood-pressure remained constant. The operation lasted about 2 hours and was made under N_2O-O_2 -ether anaesthesia with intubation and spiropulsator.

Examination of the removed lung (Fig. 1) showed:

The entire inferior lobe consisted a system of pus-filled, smooth-walled cysts of varying size, up to that of a hazel nut. Between the cysts there was an infiltrated firm tissue, by no means resembling pulmonary tissue. Apparently the bronchi were very poorly developed but did not otherwise display any signs of interest. The superior lobe was atelectatic.

In the microscopical examination of the removed lung the findings were as follows:

Lung tissue with ectatic bronchi and alveoles, and with chronic interstitial pneumonia ("cystic lung").

For the first few days after the operation the patient was lying in oxygen tent and was not dyspnoeic from then onwards. The secretion decreased evenly but slowly. Less than one month after the operation it could be ascertained by observing the movements of the column in the Bülow-flask that a distinct fixation of the mediastinum had occurred. 3 weeks after the operation he was out of bed, and after another 3 weeks the drainage tube was definitely removed. During the rest of his stay in hospital he was treated with general corroboration such as quartz-light, exercise and the like. He was discharged in complete well-being 78 days after having been submitted to pneumonectomy as the youngest patient in the world.

The case history, however, had a short postlude, for after 3 weeks' stay at home in well-being the patient was re-admitted, because a small fistula had appeared where the drainage tube had been; it had been caused by a bronchial fistula. The latter was touched with a 33 per cent. silver nitrate solution through a bronchoscope introduced under ether anaesthesia, which gave rise to an acute oedema of the glottis, requiring tracheotomy in the course of a few days. Treatment with steam tent, calcium injections and ephedrine took him safely through this complication, and about 4 months afterwards the bronchial fistula had healed completely.

An after-examination just one year after the extirpation of the lung showed completely satisfactory conditions. The boy was thriving well both physically and psychically. He had no cough and was able

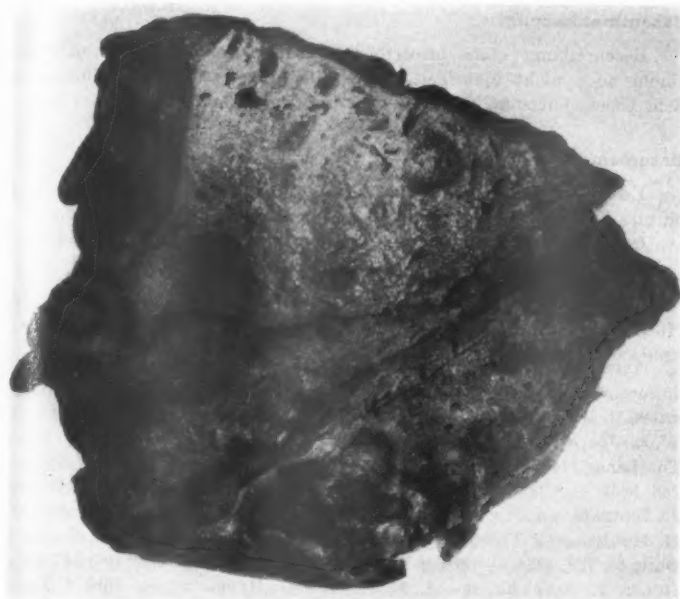


Fig. 1. $\frac{1}{1}$.

to move freely about, playing like children of his own age without becoming dyspnoeic, and no deformity of the vertebral column could be demonstrated in the clinical examination.

Summary.

A successful case of pneumonectomy in a child, just under 2 years old, with congenital cystic lung is described.

As far as it has been possible to ascertain, this is the youngest patient who as yet has passed successfully through this operation.

Résumé.

On décrit un cas traité avec succès de pneumonectomie chez un enfant âgé d'un peu plus de 2 ans avec un poumon cystique congénital.

D'après ce qu'on a pu constater ce patient est, jusqu'ici, le plus jeune qui ait subi cette opération avec succès.

Zusammenfassung.

Beschreibung eines erfolgreichen Falles von Pneumektomie bei einem noch nicht 2jährigen Kinde mit angeborener Zystenlunge, als dem bisher jüngsten, das diese Operation glücklich überstanden hat.

Resumen.

En este artículo se describe un caso afortunado de neumonectomía en un niño de poco menos de 2 años, con pulmón congénito quístico.

Que se sepa, éste ha sido el enfermo más joven que ha sufrido con éxito esta operación.

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PROCEEDINGS OF PÆDIATRIC SOCIETIES

Proceedings of the Swedish Pædiatric Society.

Edited by the secretary, **BIRGER BROMAN, M. D.**

Meeting in Stockholm, February the 14th, 1947.

Prof. A. Lööf (The Caroline Institute's Pædiatric Clinic at Norrtull's Hospital): **The weight of new-born infants past and present.**

The birth weights of 248 children born in wedlock and 497 born out of wedlock, from 1850—1860 at the General Maternity Hospital in Stockholm, were compared with the birth weights of about the same number of children born from 1935—1945 at the same institution. The material was identical as to sex, month of birth and family civil status etc.

The latter group of children weighed on an average of 300—400 grams (in wedlock) or 200 grams (out of wedlock) more than the former group of children. A tendency to increased weight pervaded throughout the different groups compared.

This weight increase in new-born infants is thought to be due to a higher standard of living, improved hygiene and more widespread popular education.

B. Hamne (Pædiatric Department of the Falun Hospital): **A case of aortic stenosis and congenital dystrophia brevicollis.** (H. Nielsen.)

A 14 year old girl suffers from breathlessness. She shows the classical symptoms of aortic isthmus stenosis. A detail worth noting is that while the blood pressure in the right arm is greatly increased (160/100 mm Hg), the systolic pressure in the left arm is normal and the diastolic increased (120/100). At the same time, the collateral circulation in the intra-costal arteries of the right side is greatly developed with distinct, palpable pulsations. Widened and lacunar rarefactions can be seen on the roentgenogram. Only very slight rarefactions are visible on two ribs of the left side. This makes one assume that the left subclavian artery is also stenosed. A section case of Nylin and Crafoord shows that stenosis can obstruct the circulation to the left subclavian artery. The electrocardiogram shows a prolonged QRS and an incomplete branch block mostly of the Wilson type. Clinical picture and prognosis are discussed.

After cardio-angiography, the case may possibly be operated on by Dr. Crafoord.

The girl also shows the following anomalies: dwarfness (height 130 cm/average 159 cm), short neck with neck wings (pterygium colli), hypogenitalism (no secondary hair-covering), hypertrichosis on head, back, and lower leg, low hair line down on back of neck with peak in center as well as over each neck wing. Elbow joint shows cubitus valgus. Unusually large distance between pupils (63 mm). Exophthalmos and slight ptosis of the eyes. In 1934, H. Nielsen pointed out the similarity of this symptom-complex to Klippel-Feil's syndrome. In the author's case, however, no change is evident in the cervical vertebral column as according to Klippel-Feil. The skull is strikingly round as seen from the front and shows «kyphosis at the cranial base» just as Klippel described in his first case.

The author describes the etiology and is inclined to interpret the following symptoms as one disease entity: aortic stenosis — Nielsen's syndrome — (in the author's case) prognathism of the lower jaw and funnel breast. The author feels that this set of symptoms is a result of hindered development and malformation in different organs even more so as several cases in literature with many similarities to Nielsen's syndrome also show muscle defects, congenital heart disease, luxation of the hip, cleft palate, club foot, situs inversus, hypospadia and Mongolian idiocy. In the author's case, the child's maternal grandmother and granduncles had short necks and neck folds. From this point of view, it is clear that the clinical picture may vary. The author feels that Turner's syndrome (infantilism, pterygium cilli, cubitus valgus) and «Status Bonnevie—Ullrick» (in Swiss literature) should be included in the same syndrome.

Marit Skatvedt (The Caroline Institute's Pædiatric Clinic at Nortull's Hospital): **The functional development of children.** A preliminary report.

Anderson Aldrich and Mildred Norvall published «A Developmental Graph for the First Years of Life» in the *Journal of Pediatrics*, September '46. A corresponding investigation has been made by the author on Swedish children. Normal children at Child Health Stations have been examined. Sufficient material for definite statistical conclusions has not been assembled as yet.

So far, the results are as follows: Swedish children

— start to smile between the 2nd and 8th week with a marked peak at 1 month.

— begin to coo and babble between 2 weeks and $3\frac{1}{2}$ months of age with a maximum at 4—8 weeks, culminating at 6 weeks.

- begin to master head balance between the 1st week and $3\frac{1}{2}$ months with a maximum at 1—8 weeks, culminating at 1 month.
- grasp at $2\frac{1}{2}$ — $5\frac{1}{2}$ months but mostly between the 3rd and 4th month.
- are able to roll completely over from $2\frac{1}{2}$ —8 months with even distribution.
- sit without support at 5—9 months with a slight peak at 6 months.
- creep at 5—11 months.
- pluck with thumb and forefinger at 7—9 months (only a small number).
- raise themselves to standing position at $6\frac{1}{2}$ —11 months.
- walk with support at $7\frac{1}{2}$ months—1 year (only a small number).
- stand upright without support at 8—13 months (only a small number).
- walk at 9—17 months with quite even distribution.

DISCUSSION: — *Wallgren*: Spoke of a yet unpublished investigation of the functional development of children over one year and showed a graph of the results. In general, children do not vary greatly except in their individual ability to control bowel movement and urinary secretion. This showed a rather great distribution.

Petter Karlberg and *John Lind* (The Caroline Institute's Pædiatric Clinic at Norrtull's Hospital): **A simple method of determining the basal metabolism of infants.**

Several methods for determining the basal metabolism of infants have been worked out in Scandinavia, especially by Råihä. No method suitable for general use has, however, yet been published. Since spring 1946, work has been going on at the Norrtull Hospital to find a practical method. Our investigations have resulted in a method the principles of which were outlined at the Northern Pædiatric Congress in Helsingfors, June 1946.

The method is based on the use of Krogh's spirometer already found at most hospitals. The infant is placed in a chamber consisting of a plexi-glass hood equipped with water lock, and an air-tight, electric bellows pump is coupled to the spirometer. The apparatus has a total volume of approximately 50 liters. Examination takes one hour. Oxygen consumption is estimated the second half hour as equilibrium of gas exchange and temperature is reached after 30 minutes. Temperature regulation is unnecessary.

The examination is made in the morning after a calory-low, protein-poor diet. A slight dose of barbituric acid is given to facilitate muscle relaxation. Double determinations have shown a difference of, at the most, 6 %. In routine examinations, a single determination is considered

sufficient. Calculation of metabolic rate is done in the usual way, preferably with the help of a nomogram. The whole procedure does not take longer than one double determination on an adult and does not demand specially trained personnel. The chamber and pump, the necessary complements to Krogh's spirometer, cost between 700—800 Swedish crowns.

DISCUSSION: — *Kaiser* described and apparatus built by *Räbba* for determining basal metabolism.

Hamne spoke of a method for determining the metabolic rate of animals.

Karlberg: The fundamental principles of the different methods are the same. The advantage of the apparatus demonstrated is that it is cheap, simple and reliable and that the regular Krogh spirometer can be used.

Walter Keller (The Caroline Institute's Pædiatric Clinic at Norrtull's Hospital): **Studies of the rapidity with which food leaves the stomach of infants.**

An adequate amount of mother's milk was given by means of a rubber stomach tube. After one hour, gastric retention was estimated by removal of the stomach contents which were immediately refilled to the original value. This was repeated several times. The author concludes that the speed with which food leaves the stomach is in direct proportion to the child's body surface. 0.1 m² body surface corresponds to an emptying speed of 22 cc mother's milk per hour. Premature and full term infants do not differ in this respect. Hunger induces a temporary increase in emptying rapidity. This explains why the stomach empties more quickly in the morning after a night without food. No other diurnal rhythm exists.

During illness, gastric activity is definitely retarded.

G. Rodhe (The Caroline Institute's Pædiatric Clinic at Norrtull's Hospital): **Lactation in young women.**

44 mothers under 17 years of age and 50 mothers over 20 were compared as to lactation capacity. The two groups were made up of women from homes for unmarried mothers. They had been admitted 1—2 months before parturition and remained until, at the outside, 9 months after. All lived under identical conditions. Socially, the material was very homogeneous. It was mostly composed of domestic help, office-employees and shop-girls, all primiparae.

The average amount of milk per day among the younger mothers was 569 g the 9th week, 468 g the 18th and 337 g the 27th week, versus 621 g, 582 g and 499 g respectively among the older mothers. The same tendency reappeared when the material was divided up in different ways

as, for example, into age groups of 15 years, 16 years, 20—23 years and 24 years. Lactation tended to increase with age.

Though the difference was proved to be statistically significant only the 27th week, the constantly reappearing tendency speaks for a somewhat inferior lactation capacity among the younger mothers.

P. Karlberg and L. Ström (The Carolinæ Institute's Pædiatric Clinic as Norrtull's Hospital): **Experiment with the Oximeter (according to Millikan's principle).**

The authors demonstrate a Swedish oximeter made by the engineering firm C. E. Berg after the same principles as Millikan's oximeter. Light absorption in red light is greater for reduced hemoglobin than for oxy-hemoglobin. If a part of the body, preferably the ear, is placed between a light source and a photo cell, the variations in oxygen saturation of the blood can be registered photoelectrically and the values read off on the galvanometrical scale, graded in percents of oxygen saturation.

With the help of the oximeter, it is possible to constantly follow the variations in oxygen saturation without taking blood samples. The apparatus may also be used for new-born infants.

An account was given of several investigations made with this apparatus at the pædiatric clinic of the Caroline Institute at the Norrtull Hospital.

DISCUSSION: *Å. Gyllenswärd*: Has made circulation time estimates with the aid of the oximeter. The patient breathes hypoxia air (9 % oxygen and 91 % nitrogen) until oxygen saturation drops to approximately 70 %. The patient then takes several deep breaths of either fresh air or pure oxygen. The time interval is measured between the first deep breath to the instant the galvanometer shows oxygen saturation beginning to rise in the blood. This time interval indicates the speed by which oxygen is conveyed from the lung to the ear. The alveoli must function normally. In this way, the time for blood to pass from the lung through the left half of the heart out to the capillary system, is determined. Experiments on normal children show this time interval to be 4—5 seconds. Sufficient study of pathologic material is as yet lacking.

O. Axén and J. Lind (The Caroline Institute's Pædiatric Clinic at Norrtull's Hospital): **Angiocardiography of infants.**

A method of angiocardiography of infants with synchronous exposure of the frontal and sagittal planes is described. An electrocardiogram is taken simultaneously. The exposure time is marked on the electrocardiographic curve so that one may know during which cardiac phase the pictures are taken. Three photographs are taken from each plane

within the space of 4—6 seconds. 70 % diodrast (5—10 ml) is used as a contrast medium. The injection is made in a jugular vein. Demonstration of angiocardiograms.

Meeting in Stockholm, March the 14th, 1947.

G. Laurell (Sachs' Children's hospital and the State Institute for Public Health): **Airborne infections: the importance of oiled floors and textiles in childrens' hospitals with special attention to dangerous carriers.**

Nosocomial streptococcal infections were studied at the Sachs' Children's hospital during the winter and spring of 1946 (Laurell, Lefström, Magnusson and Ouchterlony). In spite of their occurring both among personnel and children, secondary infections did appear under certain conditions and then generally due to a dangerous carrier. Streptococci were found at these times both in the air and dust.

The present investigation was made during the fall and winter of 1946—1947 with a view to proving what effect the treating of floors and textiles with oil would have on the spreading of nosocomial infections. The method used was the one described by Robertson and his collaborators.

The hospital where this investigation was made, consists of two wards: ward I and ward II planned completely alike. Ward II was treated with oil and ward I was used as a control. The results appear in table I.

Table 1.

| | | Num- ber | Total streptococcal infections | Secondary streptococcal infections | Secondary streptococcal infections, Per cent |
|---------------|-----------|-------------|--------------------------------------|--|---|
| Ward unit I. | Patients | 200 | 23 | 5 | 21.7 |
| Control. | Wardstaff | 38 | 22 | 11 | 50 |
| Ward unit II. | Patients | 229 | 33 | 12 | 36.3 |
| Oiled. | Wardstaff | 41 | 21 | 14 | 66.6 |

The investigation showed as follows:

1. that the number of secondary infections was not affected by the steps taken.
2. that the presence of a dangerous carrier (4 in the oiled ward versus 1 in the control ward) was of decisive importance in accounting for secondary infections.

3. that consequently, in judging the value of prophylactic measures, no conclusions may be drawn without considering the decisive importance of dangerous carriers.

J. Henning Magnusson (Sachs' Children's hospital): **Toxoplasmosis in Sweden. Two clinically-serologic diagnosed cases.**

In September 1945, a 5 day-old infant boy was admitted for blood vomiting. He weighed 2430 grams, was afebrile and otherwise in good health. Liver and spleen palpable. A series of small petechiae which faded after a few days could be seen on the front side of the trunk and the inner sides of the thighs. Thrombocyte count the day of admission, 165 000. Two days later, 255 000. Blood vomiting was due to hypoprothrombinemia and stopped after administering of vitamin K.

Because of certain symptoms, this patient has been kept constantly under control. As to height and weight, his physical development has proceeded normally. Psychical development has, on the other hand, been considerably retarded. The child is now 1½ years old and presents the following symptoms:

1. Intraventricular, garland-like calcifications at the site of the choroid plexus. Porencephalia. Internal hydrocephalus.

2. Micro-ophthalmia, somewhat more pronounced on the left than on the right side. Chronic uveitis with secondary cataract, total on the left side.

3. Psychic retardment. How large a part of this is due to cerebral deficiency and how much is caused by blindness is hard to judge.

In January 1946, when the child was a little more than 3½ months old, the clinical diagnosis of toxoplasmosis was made.

During the first half of 1946, repeated inoculations were made on suitable experimental animals with different punctates from this child. The results were completely negative as could almost be expected, toxoplasma being an intracellular parasite.

The next available chance to prove the clinical diagnosis was serologic proof of neutralizing antibodies in the patient's serum. Toxoplasma is however necessary for this test. *Dr. Abner Wolf* kindly provided me with this material for which I express my warmest thanks. The strain in use up to now is the «L. M. strain», which arrived in Stockholm January 27th, 1947.

Serologic examination was made February 24th and showed a positive result not only for the patient but also for his mother. March 10th, both were examined again with the same positive outcome.

The mother has always been in good health and because of her child's illness has recently undergone a thorough physical examination with only negative findings. Her infection has apparently been unnoticeable

without any obvious clinical symptoms. The mother is, however, a carrier and must have contaminated her child antenatally.

Serologic tests were also made on the father and on a 3 year-old sister of the patient, both with negative results.

We must therefore reckon even here in Sweden with the occurrence of human toxoplasmosis.

Birgitta Werner (Sachs' Children's Hospital): **The Protein-Digesting Enzymes. A Comparison between Premature and Full-term Infants.**

As is well-known, the addition of protein to the food of premature infants has but little favourable effect on their growth. In 1943, Magnusson started using protein hydrolyzates in the place of protein. The satisfactory results invariably obtained since then by this method, raise the question as to whether the immaturity of the proteolytic enzyme system of viable premature infants is of such a degree as to be of practical importance.

On material from Sachs' Childrens hospital and several Maternity hospitals in Stockholm the development of pepsin and pancreas proteinase secretion during the last months of foetal life has been studied in 42 premature and 19 full-term infants. The majority (32) of the premature cases were born in the eighth or ninth foetal months, their weight ranging from 1 to 2 Kg. The time of survival of the infants varied from 0 to 3 days, the average being 24 hours. The causes of death were: intervention during labour, debility, pulmonary atelectases and intracranial hemorrhage.

The value of the investigation might seem to be considerably impaired owing to the heterogeneity of the material. Thus — due to their human origin — the cases vary in length of life and cause of death. Since, however, each premature group has been compared with a corresponding full-term one, and the results obtained are, moreover, surprisingly uniform, these unavoidable errors cannot have been of decisive importance.

The gastric mucosa was treated histologically according to Bovie's method, in which the pepsinogen granules in the «chief cells» are stained dark-violet against an otherwise light-pink tissue.

The material assembled shows a marked difference between premature and full-term infants. In the latter cases, a border of coarse granules is always found in the basal part of the gastric mucous membrane, while in weight-groups below 2 300 g and still more so below 2 000 g, very few granula-containing cells are to be seen, and these only after thorough study. In weight-groups below 2 000 g it is impossible to distinguish any gradations in the granula-content, the infant weighing 1 000 g having as many — or rather as few — pepsinforming cells as that weighing

2 000 g. Just before full term, pictures characteristic of premature mucosa are seen to alternate with typically full-term ones.

Apparently, the transition from debility to full term in respect to pepsin-production does not take place gradually, but abruptly, and as late as in the 10th foetal month.

Applied to the pancreas, Bovie's method results in a similar staining of the zymogen granules. It is true that here the material does not show the same sudden change from prematurity to full term as is characteristic of the peptic cells, but the evident difference in the granulation of full-term as compared to premature cases nevertheless permits the assumption that a marked difference in functional capacity must exist.

In several cases the histological material has been controlled by chemical determination of the enzyme content. Northrop's method for quantitative estimation of the enzyme activity was used. The results obtained corresponded well with the histological picture.

Judging from the material examined, it should be advisable to add protein hydrolyzates instead of protein to the food of debile infants, since the proteolytic enzyme system reaches an effective capacity so late in foetal life.

R. Zetterström (The Sachs' Children's Hospital): **Investigation of phosphorus metabolism in young, D-avitaminotic rats by use of isotope technique.**

Young, white male rats, fed one month on McCollum's rachitogenic diet, were used as experimental animals. Phosphorus metabolism was studied after oral intake of the radioactive phosphorus isotope P 32. Of the D-avitaminotic animals, half were given 100 units of vitamin D by means of a stomach tube three hours before P 32 administration. Rats the same age as the experimental animals and raised on a normal diet, were used as controls. The animals were decapitated 40 minutes and 22 hours, respectively, after P 32-intake. As comparative figures for the organs examined, the specific activity was calculated i. e. the relation between the number of given impulses per minute from the radioactive substance and the total amount of phosphorus expressed in μg . In cases in which resorption had varied, the relative specific activity was also calculated i. e. the relation between the specific activity of the tissue in question and the specific activity of blood.

Examination showed that, after forty minutes, the phosphorus content of the stomach tissue was approximately the same for all three experimental alternatives. By that time, the controls had very likely passed their resorption maximum. After two hours, resorption was lowest in the controls. It was highest in the animals that had been fed on a rachitogenic diet but received vitamin D before the experiment. In this case, the resorption was approximately seven times greater than in the con-

trols. The value for the rachitic animal not given vitamin D before the experiment, lay approximately between the above two estimates. There was evidently retarded phosphorus resorption in the animals fed on a D-avitaminotic diet. If vitamin D was given these animals before value determination, phosphorus resorption was increased.

Examination of phosphorus resorption of the duodenum gave approximately the same result. The rachitic animals administered vitamin D before the experiment showed both after forty minutes and after two hours, three or four times greater resorption than the other two groups. After forty minutes, the value was lowest for rachitic animals not given vitamin D and after two hours, lowest for the controls. D-avitaminotic animals thus seemed to compensate for phosphorus deficiency by an increased phosphorus resorption when given vitamin D before the experiment.

The specific activity of the blood was shown to be analogous to the resorption conditions mentioned. After forty minutes, the value was approximately the same in the controls as in D-avitaminotic animals given vitamin D. This value was about seven times higher than for rachitic animals not given vitamin D.

The relative specific activity, a term for the phosphorus metabolism of the different organs, was as follows:

1. In the *kidneys*, already after forty minutes, it was three times higher for the controls than for the animals fed on a rachitogenic diet. The value was approximately the same for the two rachitic groups. After two hours, the value was highest in the animals fed vitamin D before the experiment. It seemed as if resorption, metabolism and secretion apparently occurred much more rapidly in normal than in rachitic animals. Animals raised on a rachitogenic diet and given vitamin D before the experiment seemed, in this respect, to have followed a middle course.

2. In the *skeleton muscles*, phosphorus metabolism was three times greater in rachitic animals than in the controls not fed vitamin D. The value for rachitic animals given vitamin D before the experiment was, however, the same as for the controls. Vitamin D seemed, momentarily, to be able to reduce the pathologically high phosphorus metabolism in rachitic animals to normal value.

3. In the *epiphyses*, the value was also considerably higher for rachitic animals without a previous dose of vitamin D than for the other two groups which showed about the same values. Vitamin D seemed to be able to reduce the increased metabolism very quickly here also.

4. In the *diaphysis*, controls as well as rachitic animals given vitamin D showed the same values after two hours, while the values of the other animals were only one sixth as great. Phosphate precipitation takes place in the diaphyses. The amount precipitated seems to be much

greater in normal than in rachitic animals. Vitamin D is apparently able immediately to speed up this precipitation to normal.

5. In the *thyroid gland*, relative specific activity after forty minutes was lowest in the controls. The value for rachitic animals given vitamin D was about twice as high and for rachitic animals with no extra vitamin D, about ten times as high. After two hours, approximately the same conditions prevailed. The value for rachitic animals was, however, only five times greater than for the controls. Phosphorus metabolism in the thyroid gland is therefore far higher in rachitic than in normal animals.

CONGRESS

Hungarian Centenary Congress of Pediatrics.

The Hungarian Medical Trade Union desires to celebrate the centenary of the Liberty War by arranging a medical convention in Budapest between the 4th and 12th September, 1948. In the course of this week, the Pediatric Section will organize an International Congress of Pediatrics.

Of the five days of the Congress, two will be devoted to plenary sessions of all the sections. On three days the following topics will be discussed.

Rheumatic Fever,
Toxicosis,
Social Significance and Results of Pediatrics.

Lectures on miscellaneous subjects will also be held.

All pediatricians interested in the Congress are invited to participate. Those who expect to attend the Congress should communicate with the above Committee and those who wish to take part in the discussion of one of the main topics or to present a paper on another subject are requested to give the title and short summary of their lecture.

PAUL KISS, M. D.

PETER V. VÉGHÉLYI, M. D.

Centenary Congress Committee
Bokay Janos u. 53
Budapest 8
Hungary

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REDIGENDA CURAVIT

A. LICHTENSTEIN

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EDITOR PROFESSOR A. LICHTENSTEIN

KRONPRINSESSAN LOVISAS BARNSJUKHUS,
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The 'ACTA PÆDIATRICA' contain articles relating to pediatrics. These articles are published in English, French or German, according to the wishes of the author. Each number consists of about 6 printed sheets, 4 numbers forming a volume. The numbers will be issued as soon as the articles sent in can be printed. The 'Acta' is open to articles from foreign authors in all countries, if sufficient space can be found for them. Manuscripts are to be sent direct to the Editor, to whom also enquiries about the exchanging of papers are to be directed. The subscription should be forwarded to the Editor. Each volume costs 25 Swedish crowns.

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Granulocytopenia in Children.

By

LEIF SALOMONSEN.

In the course of the last decades it has been shown that granulocytopenia (neutropenia) is a frequently occurring symptom. But still we are confronted with a poorly defined, confusing pathological conception of the condition. From an etiologico-pathogenetic point of view, quite different factors seem to be involved. Clinically, too, the symptom is heterogeneous. We see how the granulocytopenia on one hand may cause severe constitutional symptoms and end fatally. On the other hand, it may be a relatively insignificant symptom with a favourable prognosis and without serious constitutional involvement.

A pediatrician who wants to take an interest in looking up data on granulocytopenia in children in handbooks of pediatrics, will only find short and incomplete mentions of the disease, in spite of the fact that most forms of the typical granulocytopenias occur in children, especially during the first years of life.

In children the following clinical types of *pure* forms of granulocytopenia, i. e., granulocytopenias with a selective reduction in the polymorphonuclear cells as the only morphological change of the blood, may be differentiated, not considering the granulocytopenias which may occur as an associated symptom of anemia (in splenomegalias, leukemia, aplastic anemia, pernicious anemia, tumors of the bone, etc.):

1. *Parainfectious, benign granulocytopenia.* It is a well known fact that different infectious diseases may be associated with leucopenia and relative granulocytopenia. The prototype is exan-

thema subitum, and also rubeola, typhoid fever, and undulant fever. But even in banale catarrhal infections of the upper respiratory tract the same hematological changes may be seen, especially during the first years of life.

The number of leukocytes seldom drops below 2 000 or 3 000. The granulocytopenia may, especially in exanthema subitum, be very marked, but the granulocytes never completely disappear from the blood.

The granulocytopenia, as far as we know, does not give any clinical symptoms, and will regress spontaneously with the healing of the disease. The cause of the granulocytopenia is unknown. It may be due to an abnormal distribution of the leukocytes in the blood, the granulocytes collecting in the internal organs (the sinuses of the spleen?) as a phase in the effort to overcome the infection.

2. *Parainfectious, malign granulocytopenia.* An also well known clinical feature of grave infections — as an omen malum — is the usual leukocytosis being replaced by a leukopenia and relative granulocytopenia (especially in sepsis, and also in pneumonia, miliary tuberculosis, etc.).

To illustrate this, the following blood values in two children suffering a sepsis running a lethal course, are recorded:

| | Patient, aged 3 weeks | Patient, aged 3 1/2 years |
|---|-----------------------------|---------------------------------|
| Leukocytes per cu. mm..... | 1 700 | 3 500 → 760 |
| Myeloblasts, promyelocytes, per cent..... | 0 | 0 |
| Basophils, per cent..... | 0 | 0 |
| Eosinophils, per cent..... | 0 | 1 |
| Myelocytes, per cent..... | 0 | 0 |
| Metamyelocytes, per cent..... | 0 | 0 |
| Neutrophils, unsegmented, per cent..... | 6 | 0.5 |
| Neutrophils, segmented, per cent..... | 4 | 0.5 |
| Monocytes, per cent..... | 2 | 0.5 |
| Lymphocytes, per cent..... | 88 | 97.5 |

In the first patient the sternal smear showed a marked predominance of myeloblasts and only few promyelocytes, the further developmental stages of granulated cells otherwise missing. One might be attempted to consider such cases as representing aleukemic leukemias.

However, in both patients hemolytic streptococci could be demonstrated, and the postmortem diagnosis was sepsis.

This paradoxical, infectious leukopenia is usually explained as being due to a toxic exhaustion of the bone marrow.

3. *Postinfectious granulocytopenia.* As a direct result of different infectious diseases, without any medication having been instituted during the course of the disease, an acute granulocytopenia may develop (2, 4, 6, 8, 10, 14, 21, 22, 23, 24). Most frequently, banal infections of the upper respiratory tract seem to be the incitant disease. The blood shows, as the only change, a leukopenia with a relative granulocytopenia ranging as low as to complete absence of granulocytes. From the few bone marrow studies which have been carried out, it appears that a lively myelopoiesis is taking place, with a preponderance of young cells and a decreased number of mature cells («maturation arrest»). A completely aplastic bone marrow has not been described.

Reports exist of cases running a course with high fever, marked constitutional involvement, and necrotic ulcerations of the oral and pharyngeal mucosa, in some instances ending lethally. These cases must be classified as malign agranulocytosis (Schultz's type). But most commonly, the disease runs a more quiescent course with little constitutional involvement and favourable prognosis. Within some days to a couple of weeks, the granulocytopenia regresses spontaneously and the leukocytic picture again takes a normal appearance.

The condition is most common in early childhood ($1\frac{1}{2}$ to 3 years). It is quite probable that mild cases escape detection. The leukopenia of early childhood is as a rule moderate, because the granulocytopenia is compensated by the relative lymphocytosis of this age. Thus, the condition is only recognized when a differential count is carried out.

Pathogenetically, the condition seems to be due to a brief, transitory maturation arrest of the granulocytes. It is reasonable to interpret the condition as an allergic reaction to the contagious agent of the primary disease, and it can thus be compared to the postinfectious thrombopenia following rubeola, morbilli, etc.

4. *The granulocytopenia following medication* is a well known feature in adults, especially in the form of the malign agranulocytosis (Schultz's type). This condition was until few years ago regarded as extremely rare in children. Amidopyrine agranulocytosis is as far as I know not described in children at all. But the introduction of the sulfonamides has caused an increasing incidence also in children, and this indicates a serious warning against the indiscriminate use of these drugs. The clinical picture and the blood findings do not deviate from those in adults.

5. *Radiation*, as well in children as in adults, may damage the bone marrow and thus cause granulocytopenia.

6. *Primary splenogenic granulocytopenia* is an extremely rare disease (9, 16, 18). It may run a markedly chronic course. The spleen is considerable enlarged. The bone marrow is hyperplastic, but qualitatively it presents a normal picture. The granulocytopenia can be traced back to an increased destruction of leukocytes in the spleen. Cure is obtained by splenectomy.

So far, to my knowledge, only two cases (19) have been described in children, and they were not pure granulocytopenias, being associated with anemia and thrombopenia.

7. *Cyclic granulocytopenia*. Only a few cases of this peculiar condition appear in the literature. So far, I have only been able to find three cases recorded in children, all having presented symptoms from infancy (7, 13, 17).

The disease runs a chronic, protracted course, for decades. At constant intervals of three weeks, a sudden fall in the number of leukocytes takes place, associated with a marked granulocytopenia, the number of polymorphonuclear cells ranging even below 1 per cent. The absolute number of monocytes may at the same time be increased. The bone marrow shows a preponderance of myelocytes and promyelocytes, the number of more mature cells of the granulocytopoiesis being decreased. The attacks are as a rule associated with fever, headache, malaise, and frequently with stomatitis and ulcers of the oral mucosa.

The duration of the attack is a few days only. During the free intervals the blood and bone marrow present a normal pic-

ture, and the patient feels well. In two of the three children being reported on there was a history of an obstinate furunculosis during infancy.

The cause of the disease is unknown. Endocrinous, infectious, and allergic causes have been discussed. PLUM (13), based upon studies of the bone marrow, postulates that there is no disturbance of the maturation of the granulocytes, but an arrest of the granulocytopoiesis which also involves the early stages of the premature granulocytes (myeloblasts and promyelocytes).

The incidence of the disease is probably greater than that indicated by the few cases published, as many cases of the disease must be considered as never diagnosed. In several of the cases reported, the disease had persisted for years without being recognized.

8. *Chronic granulocytopenia.* In the vast majority of cases the granulocytopenia runs an acute course. If death does not occur, change to the better will take place within a short period. In some instances it may take some weeks until the blood picture becomes normal.

However, in adults some cases of *chronic* leukopenia with a relative granulocytopenia have been observed (1, 11, 12, 15, 20). As a rule, the condition is benign. A certain degree of malaise, sometimes non-characteristic pains in the precordium, back, and extremities, are described as the only subjective symptom. Objectively, except for the findings in the blood, there are no pathological signs. The leukopenia is moderate (seldom below 2 000), and the granulocytopenia is less marked than that usually found in granulocytopenias (20 to 50 per cent). I cannot find that examination of the bone marrow has been carried out in any of the cases.

In some instances the quiescent course of the disease may be interrupted by sudden attacks of granulocytopenia with alarming constitutional symptoms. This happened, for instance, to STEALY's patient, in whom the number of leukocytes during the periods apart from the attacks though was normal. This case should be distinguished as a *recurrent* form of granulocytopenia, therefore, probably related to the cyclic granulocytopenia. How-

ever, the material published in the literature has not been thoroughly enough observed and investigated to permit a clear definition of the disease.

FANCONI (3, 5) has given a brief account on two cases of «chronic, benign granulocytopenia» in children, both patients aged about one year.

One of the patients had at the age of 6 months a febrile stomatitis and conjunctivitis which were treated with 0.6 Gm. of pyramidon. When the child was 7½ months old a granulocytopenia was detected, and this remained stationary for the following months, the number of granulocytes varying between 220 and 1 600. The bone marrow showed a lively myelopoiesis with numerous myelocytes and diminution in the number of segmented granulocytes. During this period the child suffered repeated catarrhal infections, but did otherwise not present any pathological conditions. Administration of pentnucleotide, vitamin C, and blood transfusions had no effect on the granulocytopenia. On a control examination, when the child was one year old, the blood was normal.

In the other patient, from the age of 7 months till 1½ year, a persistent, moderate leukopenia with «hochgradige» granulocytopenia was diagnosed. The bone marrow was reported as normal. The general condition was unaffected except for relapsing, mild infections.

This condition, a *chronic, benign granulocytopenia*, which to my knowledge has otherwise not been described in children, can be supplemented by the following case:

B. A., a girl, born on March 19th, 1944, an only child. The family is healthy. The delivery was uneventful, and the child had no congenital malformations. The child thrived well and was apparently healthy until the age of 9½ months (Jan. 5th, 1945), when it contracted a catarrhal fever with rhinopharyngitis and bilateral maxillary sinusitis. On the fourth day of the disease she was given a single, massive dose (2 Gm.) of sulfathiazol. No other medication was used, except for a mixture of ipecacuanha. The fever remained high, between 38° and 40° C. for three weeks, then it sank lytically. The sedimentation rate was much increased.

She was hospitalized in the University Pediatric Clinic from January 19th till February 8th, 1945. The general condition was good. Except for the aforementioned catarrhal symptoms, which disappeared during the hospitalization, the physical examination did not reveal any pathological findings, especially could no enlargement of the spleen be demonstrated. The Wasserman reaction and Paul-Bunnell's reaction were negative.

The blood was normal as to the erythrocytes and thrombocytes. The only pathological finding was a marked *granulocytopenia* (cf., table 1). This granulocytopenia remained stationary for $1\frac{1}{2}$ years, although decreasing the last half year, so that on October 1st, 1946, the leukocyte values were normal again.

Even if the presentation of the leukocyte values in absolute numbers represents a large source of error, the following features must be regarded as definitely demonstrated (cf., normal values in table 2):

Slight leukopenia, caused by a selective diminution in the number of granulocytes.

Normal number of lymphocytes.

A distinct monocytosis with an increase in the absolute number of monocytes during the initial stage of the disease.

A marked granulocytopenia, the absolute number ranging from 0 to 500, the relative number varying from 0 to 7 per cent.

Normal appearance of the white blood cells.

Sternal puncture was performed twice, on January 24th and on March 2nd, 1945. The smear showed abundant hematopoietic tissue. No abnormal cells were found. The different developmental stages of the red and white cells were all normal forms. The number of megacaryocytes was normal. The distribution of the white cells (cf., table 3) did not evidence signs of maturation arrest, although the findings indicated a slight tendency towards a reduction in the mature granulocytes.

The blood picture was not influenced by acute, febrile catarrhal infections (cf., table 1). From March 12th till March 22nd, 1945, the patient suffered a high-febrile rhinopharyngitis, and on December 17th, 1945, an acute, febrile laryngitis, both times without any change in the number of leukocytes. But on January 20th, 1947, after the recovery from the granulocytopenia, there was an evident granulocytic response to an acute rhinopharyngitis.

The granulocytopenia did not respond to the administration of pentonucleotide and liver extracts.

The patient was, as long as the granulocytopenia lasted, never seriously ill, although there was marked *constitutional involve-*

Table 1.

| Date | Hb. % | RBC. | Total number of | | | | White cells per cent | | | | | |
|------|----------|------|-----------------|-------------------------------|--------|------|------------------------|--------------|-------|--------|--------|------------------|
| | | | WBC. | Gran. c. ÷ Bas. a. Eos. | Lymph. | Bas. | Myel. and Metam. | Un- segm. | Segm. | Mono. | Lymph. | Plasma cells. |
| 1945 | 80 | 4.5 | 8800 | 264 | 7480 | | | 2 | 1 | 12 | 85 | |
| | 77 | 4.4 | 12000 | 120 | 6480 | 2 | | | 1 | 43 | 54 | |
| | | | 9000 | 90 | 3960 | | | 1 | 1 | 44 | 54 | 1 |
| | | | 9000 | 90 | 3060 | | | | 1 | 34 | 64 | |
| | | | 8000 | 480 | 2080 | 1 | 1 | 2 | 3 | 26 | 66 | 1 |
| | 83 | 4.5 | 6800 | 340 | 1904 | 4488 | 1 | 1 | 3 | 28 | 66 | 1 |
| | | | 7800 | 156 | 1092 | 6318 | 1 | 1 | | 14 | 81 | 1 |
| | 81 | 4.9 | 5000 | 25 | 4425 | | | | 7/2 | 9 | 88 1/2 | 2 |
| | | | 6600 | 462 | 1452 | 4356 | | 1 | 6 | 22 | 66 | 2 |
| | 82 | 5.0 | 6200 | 186 | 806 | 5084 | | | 3 | 13 | 82 | |
| | | | 7800 | 78 | 858 | 6708 | | | 1 | 11 | 86 | 1 |
| | 85 | 4.4 | 5200 | 52 | 806 | 4212 | 1 1/2 | 1/2 | | 15 1/2 | 81 | |
| | 84 | 4.2 | 8800 | 264 | 7744 | | | 1 | 3 | 8 | 88 | |
| | 82 | 4.0 | 8600 | 86 | | | | | | | | |
| | | | 10200 | 510 | 1224 | 8160 | 1/2 | 1/2 | 1 | 12 | 80 | 1/2 |
| 1946 | | | 8500 | 0 | 595 | 7820 | | | | | | |
| | | | 7400 | 74 | 481 | 6808 | | 1/2 | | 7 | 92 | 1 |
| | | | 8400 | 0 | 2100 | 5880 | | | 1 | 6 1/2 | 92 | |
| | | | 8600 | 0 | 1118 | 7224 | | 2 | | 25 | 70 | 3 |
| | | | 7400 | 74 | 666 | 6660 | | | 1 | 13 | 84 | 3 |
| | 85 | 4.8 | 8800 | 88 | 1056 | 7568 | | | | 9 | 90 | |
| | | | 10300 | 103 | 2060 | 7828 | | 1 | 1 | 12 | 86 | 1 |
| | 87 | | 7400 | 259 | 555 | 6401 | | 1/2 | 2 | 20 | 76 1/2 | 3 |
| | | | 11000 | 110 | 1045 | 9790 | | 1/2 | 1 | 7 1/2 | 86 1/2 | 1/2 |
| | | | | | | | | | 3 | 24 | 71 | |
| | | | | | | | | | | | | |
| | 73 | 4.5 | 6900 | 483 | 276 | 6141 | | | 1 | 6 | 4 | 89 |
| | 70 | 4.4 | 7700 | 1771 | 385 | 5544 | | | 1 | 22 | 5 | 72 |
| 1947 | | | | | | | | | | | | |
| | 72 | 4.2 | 9500 | 2375 | 100 | 6745 | | 16 | 57 | 4 | 23 | |
| | | | | | | | | 3 | 22 | 2 | 71 | 1 |

Pentaneucleotide
3-10 cc. daily
(⁹/₂-¹⁴/₂)

Rhinopharyn-
gitis (¹⁵/₂-³⁷/₂)
Campolon 2 cc.
(¹⁷/₂)

Laryngitis (¹⁷/₂-¹²/₂)

Rhinopharyngi-
tis (²⁰/₂-²¹/₂)

Table 2.

Normal leukocyte values in a one year old child.

| | Total number | | Per cent |
|------------------------|--------------|--------------|----------|
| | Average | Range | |
| Leukocytes | 10 000 | 8 000—14 000 | |
| Granulocytes | 3 000 | 1 600— 5 600 | 20—40 |
| Eosinophils | 200 | 160— 700 | 2— 5 |
| Basophils | | | 0.2 |
| Monocytes | 800 | 400— 2 100 | 5—15 |
| Lymphocytes | 6 000 | 4 000— 9 800 | 50—70 |

Table 3.

Sternal smear, march 2nd, 1945, differential count.

| | | | |
|--------------------|--------------|------------------|------------|
| Myelobl. | 0.5 per cent | Basoph. | 0 per cent |
| Promyeloc. | 5.0 » » | Lymph. | 29.5 » » |
| Myeloc. | 15.25 » » | Plasma | 0 » » |
| Metamyel. | 4.75 » » | Monoc. | 2.5 » » |
| Staff c. | 9.5 » » | Retic. | 0.5 » » |
| Segment | 10.5 » » | Normobl. | 19.75 » » |
| Eosinph. | 2.25 » » | | |

ment. The child was lively and gay with good appetite before the onset of the disease, but during the granulocytopenia malaise and poor appetite were noted. She suffered repeated *catarrhal infections* associated with fever, also during a stay in the country in the summer 1945. »Two weeks in bed, two weeks up and around,» is the mother's statement. In March 1945 the child suffered a *stomatitis* with associated *aphthous ulcers* of the tongue and lips. During the spring and summer 1945 she suffered a persistent furunculosis. In the summer 1946 a marked constitutional improvement took place. She became more lively and gay, the appetite improved, and the relapsing infections ceased. Table 1 shows that this took place simultaneously with the regression of the granulocytopenia.

Comment.

As to the *cause* of the granulocytopenia in the case here referred, nothing definite can be said. During an initial febrile disease the patient was given a single dose of sulfathiazol (2 Gm.). She had previously never been treated with sulfathiazol or other medicaments. It cannot be excluded that a congenital hypersensitiveness to sulfathiazol has been present. But this explanation is the most unlikely one.

More likely the granulocytopenia is postinfectious in nature and may be classified among the postinfectious, acute granulocytopenias. We do not know for certain when the granulocytopenia started in our patient. It may of course have been present even before the onset of her first febrile disease. But the first statement of the mother, that it was in connection with this infection that the constitutional symptoms appeared, indicates that the granulocytopenia occurred after the infection.

An explanation of the *pathogenesis* of the granulocytopenia can only be based on guesswork. The bone marrow smear revealed no definite pathological changes. Also in one of the cases of FANCONI the bone marrow was alleged as normal. These findings give no hold for the granulocytopenia being due to a maturation arrest of the granulocytopoiesis.

Only the granulocytes showed a decreased number in the blood. The lymphocyte count was normal. That the leukocytopenia in our patient was less marked than that usually seen in older patients, is explained by the physiological, high lymphocyte values of early childhood. However, the initial monocytosis merits attention. It is a well known fact that monocytosis is a relatively common finding in granulocytopenias. If this can be said to be a favourable prognostic sign — as many authors state — this is in conformity to the benign course of the granulocytopenia in our patient.

Clinically, our case present the following features of interest: First, that a *complete*, peripheral agranulocytosis may exist without associated serious constitutional symptoms, and that the alarming symptoms (fever, prostration, necrotic ulcers, etc.), which

characterize the malign agranulocytosis cannot be accepted as exclusively due to the agranulocytosis, therefore.

Secondly, the lowered resistance to infection in our patient is not an astonishing, but still an interesting feature. It is remarkably that this lowered resistance in our patient, as well as in patients with cyclic granulocytopenia, is manifested by a furunculosis. The possibility of such a pathogenesis ought may be to be considered in cases of persistent furunculosis in non-dystrophic infants.

There is a striking resemblance between our case and the two cases described by FANCONI. Comparing these cases, one is here apparently confronted with the picture of a separate disease, characterized by the following features:

- 1) Chronic, marked, selective granulocytopenia with a correspondent leukopenia.
- 2) Normal bone marrow.
- 3) Lowered resistance to infection, but otherwise little constitutional involvement.
- 4) Resistance to medicaments commonly employed in the treatment of granulocytopenias (folic acid was not available during our patient's illness).
- 5) Spontaneous cure.

The age of the child may play a part. It is note worthy, that all the three patients got their disease in the second half year of life. The same predilection to this age is also seen in the acute, post-infectious granulocytopenia.

Summary.

A short survey is given on the different forms of granulocytopenia in children. In this connection a case of benign granulocytopenia of $1\frac{1}{2}$ years' duration in a one year old child is reported. In the authors opinion, chronic, benign granulocytopenia in children of the age of about one year should be considered as a separate disease, characterized by the symptoms indicated in the five aforementioned items.

Résumé.

On donne un bref aperçu des différentes formes de granulocytopenie chez des enfants. On mentionne un cas de granulocytopenie bénigne d'une durée d'un an et demi chez un enfant d'un an. L'auteur est d'avis que la granulocytopenie bénigne et chronique chez des enfants d'un an environ devrait être considérée comme une maladie séparée qui est caractérisée par les symptômes indiqués dans les 5 faits mentionnés ci-dessus.

Zusammenfassung.

Es wird eine kurze Übersicht der verschiedenen Formen der Granulozytopenie bei Kindern gegeben und ein gutartiger Fall von $1\frac{1}{2}$ Jahre Dauer bei einem einjährigen Kinde beschrieben. Nach der Meinung des Autors ist die chronische benigne Granulozytopenie bei Kindern im Alter von ca 1 Jahr als eine besondere Krankheit aufzufassen, deren charakteristische Symptome in 5 Punkten zusammengefasst wurden.

Resumen.

En este artículo se estudian diversas formas de granulocitopenia infantil. Con este motivo se detalla un caso de granulocitopenia benigna de una duración de $1\frac{1}{2}$ años en un niño de un año. Según la opinión del autor la granulocitopenia crónica y benigna de niños de aproximadamente un año de edad se debe considerar como una enfermedad separada, caracterizada por los síntomas indicados en los correspondientes cinco puntos.

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Investigations into the Connection between Antenatal Weight and Hydrocele testis in Infants.

By

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In the course of an examination of the records of the Maternity Department for another reason it was observed that the frequency of Hydrocele testis among newly-born infants was remarkably high for children with a high weight at birth. As this does not seem to have been noticed earlier in the literature, a publication of the details of the observation seems called for.

The material comprises 484 cases of Hydrocele testis (257 dexter 96 sinister, 121 duplex and 10 with no localization stated) among 27 613 living male children discharged during the years 1910 to 1945 inclusive. The distribution of the antenatal weight is calculated with intervals of 250 g and is shown in Table 1 together with the control material, which consist of the birth weight of all living male children discharged in the years 1915, 1920, 1925, 1930, 1935, 1940 and 1945, a total of 5 593.

The table shows that hydrocele is most frequent in the heaviest weight groups, a fact which becomes more evident on taking the percentage of children weighing over 3 800 g. For the hydroceles this value is 31.0 % as against 17.7 % in the control material. The last column is an index calculated as the ratio of the percentage of children with hydrocele and the percentage of children in the control material for the particular weight group, so that it indicates how many times more frequent hydrocele is in this weight group than in the material as a whole.

Nothing can be said about the relative frequency of hydrocele testis in the newly-born children, as the number of cases has been

Table 1.

| | Hydrocele testis | | Control material | | Index |
|------------------------|------------------|------|------------------|------|-------|
| | No. | % | No. | % | |
| Under 2000 g | 16 | 3.3 | 164 | 2.9 | 1.13 |
| 2050—2250 | 10 | 2.1 | 128 | 2.3 | 0.90 |
| 2300—2500 | 7 | 1.5 | 220 | 3.9 | 0.36 |
| 2550—2750 | 22 | 4.6 | 449 | 8.0 | 0.57 |
| 2800—3000 | 37 | 7.7 | 704 | 12.6 | 0.61 |
| 3050—3250 | 58 | 11.8 | 990 | 17.7 | 0.67 |
| 3300—3500 | 107 | 22.1 | 1 076 | 19.3 | 1.15 |
| 3550—3750 | 77 | 15.9 | 870 | 15.6 | 1.02 |
| 3800—4000 | 65 | 13.4 | 565 | 10.1 | 1.33 |
| 4050—4250 | 36 | 7.5 | 251 | 4.5 | 1.65 |
| 4300—4500 | 33 | 6.8 | 114 | 2.0 | 3.37 |
| 4550—4750 | 10 | 2.1 | 47 | 0.8 | 2.45 |
| Over 4800 | 6 | 1.2 | 15 | 0.3 | 4.56 |

(The index is calculated with the use of two decimals in the percentages.)

subject to fluctuation from year to year, which means that we must reckon with periods in which the recording of this rather insignificant affection has been defective.

There is nothing about hydrocele in the obstetric text-books and manuals, whereas those on paediatrics (1, 4, 8) say that it is a fairly common affection among infants. It is often observed at birth and in the great majority of cases terminates in spontaneous cure in a short time.

In several instances the factors that are indicated as being concerned in the aetiology of Hydrocele testis are stated to be aetiological for the disease in the infant. For example, Tobler (8) often observed an inflammatory state and eczema around the genitals of these children; but it is scarcely imaginable that an unspecific inflammation can be the cause of hydrocele already present at birth. Among chronic inflammations, syphilis is credited with aetiological significance by several Italian authors (2, 6), though their observations are not convincing and others (5) have

been unable to verify this find. In the present material, syphilis was found in 11 mothers prior to or during pregnancy, but only one child definitely had syphilis.

In the Real-Encyclopädie (7), parturition trauma is given as a cause (*partus praecipitatus*, expression). This may be the explanation of the higher frequency among the heavier children, in which case it is possible that breech-presentation is likely to engender more testicle trauma. Breech-presentation amounts to 5.5 per cent. of the material (24 cases + 3 versions), a figure which cannot differ much from the usual percentage of a maternity department. If a protracted downbearing stage were of any importance one would expect a higher frequency of hydrocele in fist-born children. That this is not the case can be seen from Table 2, in which the control material comprises all living male children discharged from 1910 to 1945 inclusive.

Table 2.

| | Children with hydrocele | | Control material | |
|----------------------|-------------------------|------|------------------|------|
| | No. | % | No. | % |
| Primipara | 278 | 57.4 | 16 876 | 61.1 |
| Pluriparae | 206 | 42.6 | 10 737 | 38.9 |

There was one case of *partus praecipitatus* and four cases in which the birth lasted less than two hours, while expression was performed 14 times. It is possible that children born with the aid of forceps had a more traumatic passage through the birth canal; the forceps were used 17 times. These figures from the material of a maternity department hardly favour the argument of traumatic aetiology.

Hydrocele testis having been observed in cardiac and renal affections, it was thought that perhaps albuminuria in the mother might be the cause of reduced serum proteine in the foetus with a consequent tendency to oedema. In that case one would have anticipated a more frequent duplex localization than the 27 % found in this material. However, the material was examined for albuminuria and oedema in the mother; the result was 109 cases

of albuminuria, 53 of them being merely traces; there were only two cases of eclampsia so that the high excretion of albumin did not affect the material; the two patients had universal oedema, but otherwise the only oedema observed in any mother was of the crural type and in 89 cases, 60 of which were slight.

If nevertheless we reckoned syphilis, partus praecipitatus, expression, forceps-delivery and albuminuria (excluding traces of albumin) as being aetiological, there would still be 348 cases (71.9 %) with no aetiology, and here the distribution between children over and under 3800 g is approximately the same as in the material as a whole, viz. 32.8 and 67.3 % respectively. But as these factors are not definitely aetiological, there is neither support for nor contradiction of the theory that the more severe trauma to which large children are exposed during birth is the cause of the hydrocele in these children.

Thus the only conclusion to be drawn is that Hydrocele testis among newly-born is most frequent among the large children; the cause of this is unknown, and the aetiology otherwise is uncertain.

Summary.

Among 27 613 living male children discharged from the department there were 484 cases of Hydrocele testis; in 31.0 % of these cases the antenatal weight was over 3 800 g compared with 17.7 % in a control material of 5 593 living male children discharged. The aetiological factors concerned in hydrocele are considered and the author finds no support for the suggestion that syphilis, albuminuria in the mother or labour trauma have anything to do with its aetiology; no reason for the increased frequency among large children can be found.

Résumé.

Parmi 27 613 enfants masculins vivants il y avait 484 cas de hydrocèle testiculaire; dans 31.0 % de ces cas le poids ante-natal était de plus de 3 800 g comparé à 17.7 % d'un matériel de contrôle de 5 593 enfants masculins vivants. Les éléments étiologiques se rapportant à l'hydrocèle sont considérés et l'auteur ne

trouve aucun appui à la supposition que la syphilis, l'albuminurie chez la mère, ou la traumatisme dû à l'accouchement ont affaire à son étiologie. On ne trouve aucune raison d'augmentation dans la fréquence parmi les grands enfants.

Zusammenfassung.

Unter 27 613 lebend geborenen Knaben der Abteilung gab es 484 Fälle von Hydrocele testis; 31 % dieser Fälle hatten ein vorgeburtliches Gewicht von mehr als 3 800 g im Vergleich zu 17,7 % eines Kontrollmaterials von 5 593 lebend geborenen Knaben. Bei der Untersuchung der die Hydrocele betreffenden ätiologischen Faktoren fand der Autor die Annahme, dass Syphilis, Albuminurie der Mütter oder ein Geburtstrauma etwas damit zu tun haben, unbegründet. Eine Ursache für die vermehrte Anzahl der Fälle bei grösseren Kindern konnte nicht gefunden werden.

Resumen.

De los 27 613 niños varones que salieron de este departamento había 484 casos de hidrocele testicular; en el 31,0 % de estos casos el peso antenatal fué superior a 3 800 gramos, en comparación con 17,1 % que figura en el material de control de 5 593 niños varones vivientes que han salido. Se toman en consideración los factores etiológicos en la hidrocele y el autor no encuentra apoyo en defensa de la hipótesis de que la sífilis, la albuminaria de la madre o trauma del parto tienen algo que ver con la etiología. No se encuentra ninguna razón que explique la mayor frecuencia entre los niños grandes.

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Choline in Plasma in Children, **with a study of induced choline deficiency.**

By

GUNNAR BRANTE and LARS SÖDERHJELM.

In the beginning of the 1930:ies BEST showed that choline could prevent the production of fatty livers in rats kept on a diet, which was partly synthetic. Later it became evident that the deficiency in the diet was essentially a deficiency of methyl groups, necessary for certain methylations in the organism. Choline can be synthesized in the animal organism through methylation of ethanolamine (STETTEN 1941). The so-called »labile methyl groups» necessary for this methylation can be derived from the indispensable amino acid methionine, which was shown *in vivo* through experiments with isotopes (DU VIGNEAUD et al. 1941, STETTEN 1942) and confirmed *in vitro* through experiments with surviving liver slices (STEENSHOLT 1945). If there is a lack of »labile methyl» in the diet, deficiency signs occur, of which the fatty liver was observed and studied at first.

Choline is active in at least two different ways

1) as a methyl donor to certain acceptors (DU VIGNEAUD 1939 & 1940)

2) as a component of physiologically important compounds such as acetylcholine and the choline containing phospholipids (lecithin and sphingomyelin).

The lipotropic action of choline depends upon choline being incorporated in the phospholipids. This is clear from the fact that both arsenocholine and triethyl choline show lipotropic activity without being methyl donors, and both have been found incorpor-

ated in the phospholipid molecule after administration to rats (WELCH 1936, CHANNON & SMITH 1936, MAC ARTHUR 1946). Choline accelerates the phospholipid metabolism of the liver (PATTERSON et al. 1944, BOXER & STETTEN 1944), (but does not necessarily increase the amount of phospholipids in the liver (BRANTE 1943)), probably thereby promoting the transport of fat from the liver (STETTEN & SALCEDO 1944).

One of the most important methylation processes in the organism is the methylation of glycocholine (guanido acetic acid) to creatine. Glycocholine is formed in the kidneys (BORSOOK & DUBNOFF 1941) from arginine and glycine (BLOCH & SCHOENHEIMER 1941) and the methylation to creatine takes place in the liver. This methylation cannot be carried out to a normal extent if there is a deficiency in labile methyl groups (STETTEN & GRAIL 1942).

Most investigations in the metabolism of labile methyl groups have been carried out on rats. Chicks are not able to use the labile methyl of methionine for choline synthesis. Concerning human metabolism DU VIGNEAUD & SIMMONDS 1942, showed that a man who got methionine with deuterium in the methyl groups had deuterium in the choline in plasma and in the urinary creatinine. The methyl metabolism of man thus seems to agree with that of the rat. Recently HOBBERMAN et al. (1946) gave glycocholine to patients with cirrhosis of the liver and found that glycocholine was not methylated to a normal extent. This may be attributed to deficiency of choline or methionine, or to a diminished activity of the enzymes in the injured liver (HANDLER & BERNHEIM 1942).

GRIFFITH & WADE 1939 observed a hemorrhagic degeneration of the kidneys in weanling rats kept on a diet insufficient in choline. This degeneration was in many cases fatal, but could be prevented by adding choline, methionine, or betaine to the diet. These investigations have been confirmed by others, *i. al.* ABDON 1936, who shows, moreover, that there is not only hemorrhages in the kidneys but also a general tendency to bleeding. WELCH 1941 and DU Vigneaud & MOYER 1942 showed that triethylcholine or arsenocholine may prevent the hemorrhagic degeneration. This is therefore not ultimately caused by a deficiency in methyl but by a decreased phospholipid metabolism in the kidneys. MCHENRY

& PATTERSON 1942 have found a lower content of phospholipids in the kidneys with hemorrhagic degeneration than in normal kidneys, which fact they attribute to the decreased formation of phospholipids in the liver.

The acute glomerulonephritis in man has certain trends in common with the hemorrhagic degeneration in young rats. BADGER found in 1941 that choline is a necessary food factor for *Pneumococcus* III. Other bacteria may probably need and thus consume choline for their growth. A glomerulonephritis after a streptococcal infection might be related to a deficiency of choline, especially in children. In order to find out if there is such a relation, we have determined the total choline content of plasma in children with acute nephritis. In ascertaining the normal variations of the choline content, the same determinations were made in children with other diseases and in healthy children. We used BEATTIE's method with certain modifications i. e. extraction of heparin plasma with alcohol-ether, hydrolysis with $\text{Ba}(\text{OH})_2$, precipitation with Reinecke's salt at pH 8—9 (cfr GLICK 1944) and determination of the choline reineckate in acetone solution photoelectrically. Double estimations in 1 ml of plasma. This is a relatively accurate method and a detailed study of the influence of varying pH will be published later by BRANTE. Using this method normal values in healthy young men agree with those given by BRANTE 1940: 17.8—28.6 mg per 100 cc with an average of 24 mg %. In table I our results are given.

Umbilical cord blood from new born babies showed a low choline content, 7—14 mg% (14 observations) in agreement with the low total phospholipids in plasma of the new born. Three cases of acute nephritis in healing had 22, 23 and 26 mg% respectively. Acute nephritis and one case of chronic nephritis usually had high normal or elevated choline content of plasma as is shown in table II. (The determinations on one and the same patient were done every 14 days, the first sample taken as soon as possible after the admission into the hospital).

These elevated values are completely in accordance with the elevation of the lipids, including the phospholipids, which as a rule is found in acute or chronic glomerulonephritis. A closer analysis

Table I.

Average: (9, 10 and 18 disregarded): 25 mg %.

| No. | Age, year | Sex | Diagnosis | Choline in plasma |
|-----|---------------------------------|-----|-----------------------|-------------------|
| 1 | 12 | m | Psychopathia | 32 mg % |
| 2 | 1 | f | Healthy | 28 |
| 3 | 10 | f | Bronchopneumonia | 26 |
| 4 | 3 | f | Aerodynia | 26 |
| 5 | 2 | f | Healthy | 26 |
| 6 | 11 | m | Polyarthritis ac. | 24 |
| 7 | 12 | f | Healthy | 23 |
| 8 | 10 | f | Hepatitis subchron. | 23 |
| 9 | No. 8 after a diet rich in eggs | | | 27 |
| 10 | " " choline therapy | | | 27 |
| 11 | 12 | m | Diabetes mell. | 23 |
| 12 | 2 | f | Convulsiones | 22 |
| 13 | $\frac{3}{4}$ | f | Hydrocephalus | 22 |
| 14 | 10 | f | Erythema nodosum | 22 |
| 15 | 11 | f | Diabetes mell. | 21 |
| 16 | 10 | m | Diabetes mell. | 18 |
| 17 | $1\frac{1}{2}$ | f | Fibrosis of pancreas? | 18 |
| 18 | 5 | m | Celiac disease | 14 |

Table II.

| Name | Age, year | Sex | Choline in plasma in mg % |
|--------------|-----------|-----|---------------------------|
| C. R. . . . | 5 | f | 38; 40; 42; 41; 39. |
| C. H. . . . | 6 | f | 21 |
| L. F. . . . | 7 | f | 37 |
| G. L. . . . | 8 | m | 28; 31; 30. |
| M. H. . . . | 8 | f | 31; 24; 26; 23. |
| B. M. L. . . | 8 | f | 36; 33. |
| B. U. . . . | 14 | f | 39 (Nephritis chron.) |

of the lipids in plasma in certain cases gave the following results (Table III). (The patient C. R. was a grave nephritis with low diuresis and high N.P.N. for about 14 days, followed by a slow improvement. The other cases of acute nephritis were all less grave).

Table III.

| Name | Total lipids | Phospho-lipids | Choline-phospho-lipids | Choline-phospho-lipids | |
|---------------------------------|--------------|----------------|------------------------|------------------------|-----------------|
| | | | | Total phospho-lipids % | Freecholesterol |
| C. R. | 1 877 mg % | 319 mg % | 237 mg % | 74.3 | 114 mg % |
| G. L. | 930 | 207 | 168 | 81.2 | 54 |
| M. H. | 620 | 209 | 110 | 52.6 | 39 |
| B. U. | 1 427 | 274 | 214 | 78.1 | 94 |
| Normal values acc. to BRANTE | | 168—212 | 128—169 | 61—95 | |

The variations of the choline, not combined with lipids, are with every probability not revealed in our investigations, as this free choline constitutes such a small part of the total choline in plasma. ABDON found that a form of choline, not bound to lipids, disappears early in choline deficiency. In animal experiments, former investigators have found that plasma phospholipids are unchanged in choline deficiency with fatty livers. We have ourselves observed in cats with fatty liver (but no kidney degeneration) caused by choline deficiency normal or rather elevated total lipid and phospholipid content of plasma. Moreover, in a child (*vide infra*) with probable choline deficiency no typical changes of plasma phospholipids were observed. Thus an investigation in the total choline content of plasma cannot prove a choline deficiency unless the deficiency is so advanced that the production of choline phospholipids to plasma is greatly decreased. This may be the case in choline deficiency with kidney degeneration — we have not been able to find in literature any analysis of plasma phospholipids in that condition. A determination of free choline in plasma would give earlier results, but we have in this moment no method to our disposition. Our isolated determinations of the choline content of plasma do not, of course, tell us anything about the choline content of the kidneys. However we venture to say that our results do not favour the belief that a deficiency in choline is essential in acute nephritis in children.

In order to find out if a choline deficiency may appear in

children, we have given to a 9 months old girl, a freak with *Hydrocephalus int.* and other deformities, and no capability of maintaining life, glycoeyamine as a «methyl drainage» (glycoeyamine was used in the same purpose earlier by STETTEN & GRAIL 1942). During the experiment we almost daily determined the urinary excretion of creatine and creatinine and about every 10 days the plasma lipids. The patient could not swallow and was fed through stomach tube the same amount of water and food every day. The diet consisted of water 300 g, milk 300 g, «maizena» flour 12 g, sugar 15 g, butter 50 g, and the usual addition of A- and D-vitamins. She weighed about 8 000 g and gained in weight on this diet. The dietary content of labile methyl reckoned as choline is about 0.11 g daily (according to ENGEL 1943).

The patient got altogether 120 g glycoeyamine in daily doses of 0.5—2 g. The amount of creatine in the urine was before the start of the experiment about 0.1 gm/24 hrs, creatinine about 0.25 gm. After the administration of glycoeyamine these amounts increased practically parallell to the glycoeyamine given. The biggest daily dose, 2 g, gave an excretion of about 0.8 g creatine and 1.2 g creatinine, *i. e.* practically all the glycoeyamine was methylated. In spite of this enormous methyl consumption — 0.25 g methyl daily or about 0.67 g choline (the average consumption for adults is 0.3—0.5 g choline a day acc. BORGLIN 1947) — during a period of 8 weeks, the choline content of plasma was practically unchanged, varying between 21 and 32 mg% with a little lower values towards the end of the experiment. The other lipid fractions of plasma were normal altogether. No clinical signs of hepatic or renal injuries were observed. (Table IV)

McKIBBIN, THAYER & STARE 1944 found that dogs on a diet poor in choline showed, as the first sign of choline deficiency, an increase in plasma phosphatase, impaired bromsulphalein elimination, and a fall in blood plasma cholesterol esters. In severe choline deficiency other signs of impaired liver function appeared such as an increase in prothrombin time, and a decrease in blood hemoglobin, hematocrit, and plasma proteins. In our investigation we controlled regularly these values except hematocrit and bromsulphalein elimination, whereas other liver function tests were

Table IV.

| Date | Glycocy- amine g/day | Creatine excreted g/day | Creatinine excreted g/day | Thymol un. | Phospha- tase units | Total lipids in mg % | Phospho- lipids mg % | Choline mg % | Free cho- lesterol mg % | Total cho- lesterol mg % |
|---------------|----------------------------|-------------------------------|---------------------------------|---------------|---------------------------|----------------------------|----------------------------|-----------------|-------------------------------|--------------------------------|
| 11.10. | 0 | 25 mg % ¹ | 55 mg % ¹ | 1.8 | 7 | 800 | 166 | 28 | 46 | — |
| 23.10. | 0.5 | — | — | 0.8 | 7 | 610 | 156 | 27 | 47 | — |
| 28.10. | | 120 mg % ¹ | 180 mg % ¹ | 1.7 | 11 | 710 | 167 | 26 | 47 | 157 |
| 31.10. | | 190 mg % ¹ | 290 mg % ¹ | 1.6 | 11 | 760 | 193 | 25 | 53 | 138 |
| 4.11. | 0 | 0.4 | 0.5 | 1.1 | 12 | — | — | — | — | — |
| 7.11. | | 0.4 | 0.5 | 1.5 | 13 | — | — | — | — | — |
| 11.11. | | 0.3 | 0.7 | 1.2 | 5 | 680 | 192 | 28 | 52 | 139 |
| 15.11. | 1.0 | 0.4 | 0.6 | — | 9 | 710 | 197 | 33 | 57 | 180 |
| 25.11. | | 0.1 | 0.25 | 0.7 | 7 | 670 | 170 | 30 | 52 | 152 |
| 2.12. | | 0.6 | 0.8 | 0.7 | 8 | 600 | 146 | 32 | 46 | 126 |
| 9.12. | 2.0 | 0.6 | 0.8 | 1.1 | 7 | 580 | 148 | — | 42 | 134 |
| 16.12. | | 0.7 | 0.9 | 2.5 | 5 | 560 | 153 | — | — | — |
| 23.12. | | 0.9 | 1.2 | 2.6 | 13 | — | — | — | — | — |
| 30.12. | 1.5 | — | — | 3.1 | 16 | 700 | 166 | 25 | 47 | 136 |
| 3.1. | | 0.9 | 1.1 | 3.5 | 14 | 660 | 146 | 28 | 41 | 111 |
| 13.1. | | 0.4 | 0.7 | 3.6 | 11 | 730 | 158 | 30 | 54 | 136 |
| 17.1. | 2.0 | 0.6 | 0.8 | 2.8 | 14 | 850 | 173 | 29 | 62 | 176 |
| 24.1. | | 0.7 | 0.9 | 1.5 | 14 | — | — | — | — | — |
| 29.1. | | 0.8 | 1.0 | 2.2 | 10 | 620 | 148 | 24 | 43 | 122 |
| 6.2. | 0 | 0.1 | 0.26 | 3.1 | 7 | 480 | 140 | 21 | 29 | 110 |
| Normal range: | | | | < 4 | < 12 | 500—900 | 168—212 | 18—32 | 35—65 | 100—250 |

¹ Content in a single (not the whole day's) urine sample.

performed. After about one month of methyl drainage the plasma phosphatase rose to 13—14 units and the thymol test acc. to MACLAGAN to 3—3 $\frac{1}{2}$. On rare occasions HANGER's cephalin flocculation test was positive, but prothrombin time, plasma cholesterol and cholesterol esters, hemoglobin, the amount and osmotic resistance of erythrocytes were normal all the time. No tendency to bleeding, no decrease in plasma proteins.

One week after the end of the experiment (our limited supply of glycoeyamine was consumed) the patient died in an aspiratory bronchopneumonia. The autopsy showed no renal changes but a fatty liver in a fresh state containing 11.4 % total lipids and 1.74 % phospholipids, 63 % of which were choline containing. The last two values are to be looked upon as normal. The brain was very hydropic, but here too 63 % of the phospholipids contained choline.

Supposing the methyl group of creatine is derived exclusively from the body supply of labile methyl this experiment shows that a great methyl consumption is needed to provoke signs of choline deficiency in man. The consumption seems so great that such a deficiency may not appear other than under very unfavourable circumstances. On the other hand a decrease in the phospholipid metabolism with symptoms like those of choline deficiency may depend upon other causes than a negative labile methyl balance, e. g. enzyme disturbances through toxins and liver damages. The question of whether there is, in human nosology, a choline deficiency syndrome, endo- or exogenous, which motivates administration of choline, has been the object of much clinical research during later years. Generally speaking, it seems to us, in the light of the results of our investigation — the first of its kind — and of the extensive occurrence of labile methyl in food, that an extra choline supply to human diet will seldom prove necessary. However, the problem deserves further investigation.

Summary.

The total choline content (= mainly lipid bound choline) in plasma in children is the same as in adults, or 18—32 mg %. In new born babies it is only 7—14 mg %, whereas in acute nephritis

in children there is often an elevation of all lipid components of plasma including the choline containing.

An attempt to provoke choline deficiency in an infant through giving large doses of glycocyamine did not, in spite of great labile methyl losses, lead to any changes of the choline content of plasma, but gave a mild fatty liver with normal choline content in the phospholipid fraction. The plasma phosphatase was slightly increased and there was a tendency to positive thymol- and cephalin flocculation tests but for the rest no signs of impaired liver or kidney function. A choline deficiency in man probably appears only in very unfavourable circumstances.

Résumé.

Le contenu total de choline (= principalement lipid bound choline) dans le plasma chez les enfants est le même que chez les adultes, c'est à dire 18—32 mg%. Chez les nouveaux-nés il est seulement de 7—14 mg%, tandis que dans des cas de néphrite aiguë chez les enfants on note souvent une élévation de toutes les parties lipid du plasma, y compris le contenu de choline.

Un essai de provoquer un manque de choline chez un enfant en lui donnant de fortes doses de glycocyamine ne produisit pas de changement dans la quantité de choline dans le plasma, malgré de grandes pertes de méthyle labile, mais il s'ensuivit un foie faible et gras avec un contenu normal de choline dans la fraction phospholipid. La phosphatase dans le plasma avait augmenté légèrement et il y avait une tendance de tests de floculation de thymol et de cephalin positifs, mais pas de signes de dérangement dans la fonction du foie ou des reins. Un manque de choline chez l'homme ne se présente probablement que dans des circonstances très défavorables.

Zusammenfassung.

Der totale Cholingehalt des Plasmas ist bei Kindern derselbe wie bei Erwachsenen d. h. 18—32 mg%, bei Neugeborenen nur 7—14 mg%. Bei akuter Nephritis besteht oft eine Erhöhung aller lipiden Bestandteile des Plasmas, einschliesslich des Cholingehaltes.

Ein Versuch, bei einem Kinde einen Cholinmangel hervor-
zurufen durch Zufuhr hoher Dosen Glycoeyamin, ergab trotz
grosser Verluste an labilem Methyl keine Änderung des Cholin-
gehaltes im Plasma, hingegen eine Fettleber mit normalem Gehalt
an Cholin in phospholipider Fraktion. Die Plasmaphosphatas-
war etwas höher und es bestand Neigung zu positiver Thymol-
und Cephalin-Flockungsprobe. Im Übrigen zeigte sich keine
Behinderung der Leber und Nierenfunktion. Ein Cholinmangel
kommt wahrscheinlich nur unter sehr ungünstigen Umständen vor.

Resumen.

El contenido total de colina (principalmente colina combinada
con lípido) en la plasma de los niños es el mismo que en los adultos,
o sea 18—32 mg%. En niños recién nacidos el contenido de colina
es sólo de 7—17 mg%, mientras que en niños con nefritis aguda se
observa muchas veces un aumento de todos los componentes
lipoideos de la plasma, inclusive la colina.

El intento de disminuir el contenido de colina en los niños,
dándoles una gran dosis de glicociamina, a pesar de las grandes
pérdidas de metilo lábil, no condujo a ningún cambio en el con-
tenido de colina de la plasma, pero se obtuvo así un hígado leve-
mente graso con un contenido normal de colina en la porción fos-
folipoidea. La fosfatasa de la plasma sufrió un ligero aumento y
se notó una tendencia a pruebas positivas de floculación de timol
y cefalina, pero por lo demás no se observó ningún indicio de que
alguna función del hígado o de los riñones hubiera salido perjudi-
cada. En el hombre se presenta sólo deficiencia de colina en
circunstancias en extremo desfavorables.

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Antistreptolysin Titre in School Children.

By

GÖSTA TUNEVALL.

In spite of the great importance of the streptococcus diseases in childhood the antistreptolysin titre (AST) has not been used as extensively in pediatric work as within adult medicine. One reason may be the technical difficulty of using serological reactions as a routine in children, as sufficiently large blood samples can not be obtained as easily as from adults. More important, however, is the difficulty of evaluating an AST value correctly in a child. The first-mentioned trouble nowadays is eliminated as the reaction requires only 0.05 ml serum. The second difficulty, on the other hand, still remains since comparatively little research has been done in connection with AST in health and disease in children of different ages, therefore making it difficult to evaluate results correctly.

Most normal and control groups previously reported consist solely or almost solely of adults. Some of the more well-known studies on AST, dealing exclusively with results obtained from adults, may be mentioned, published by TODD (1932), MYERS and KEEFER (1934), MORALES-OTERO and POMALES-LEBRON (1934), BLAIR and HALLMAN (1935), LONGCOPE (1936), BUNIM and McEWEN (1940), WINBLAD (1941) and LÖFGREN (1946).

However, some authors have investigated AST even in children. COBURN and PAULI (1935) in a small series found a tendency to higher values in children than in adults of the same population. This tendency is still more pronounced in a larger group (316 children aged less than 15 years and 153 adults), reported by

GORDON and BALTEANU (1938). In this series 23 per cent of the children had AST over 100, compared with 14 per cent of the adults. According to a study of the distribution of AST by WESTERGREN and STAVENOW these figures should correspond to resp. 5 per cent and 3 per cent over 200. Another group, investigated by MOTE and JONES (1941), presents similar proportions. Of 698 children under 16 years 30 per cent had AST values over 150, while only 9 per cent of 113 adults exceeded that limit. These figures, in the same way, should correspond to 15 per cent resp. 3 per cent over 200. Elevated values were more common between 6 and 10 years than in other age groups. Finally, KALBAK (1942) reports on 99 children under 16 years. Of these, 16 per cent had AST over 200, compared with 6 per cent in a similar series consisting of adults. Even in this group elevated titres are most common in the ages from 6 to 10 years (25 per cent).

Of other investigations of AST in children a study by LIPPARD and JOHNSON (1935) only comprised preschool children while WILSON, WHEELER and LEASK (1934) reported a study, according to which children between 6 and 10 years of age present mainly higher values than children of both younger and older year classes.

On the whole the investigations mentioned indicate a higher frequency of elevated AST values in children clinically free from actual infection with hemolytic streptococci, than in healthy adults within the same population. This tendency is especially marked in school children. Literature on infections in which hemolytic streptococci play an important role, as sore throat, scarlet fever, rheumatic diseases and so on, is abundant but AST following the common upper respiratory infections most frequent in the school ages has received very little attention. Nor do these investigations give any information concerning AST in Swedish school children, in our climate and in our milieu of infection.

Author's Investigations.

The series now reported comprises 103 children registered at the Institute for Blind Children, Tomtebodavägen, Stockholm. The

children were from 7 to 16 years old, and the age distribution in the series was fairly even.

Apart from their reduced vision the children did not present any anomalies. Some features of the childrens' living conditions important for the evaluating of the investigation, ought to be mentioned. During the first years at the institute the children are located in dormitories, accomodating up to 10 pupils. Later on the children live in rooms for 6—4—2 inhabitants. During class work and spare time the children live just as other school children.

The medical observation of these children always is very careful, according to the demands in an internate. All infections, even very simple ones, are registered. Now for one year this regular observation was completed in several respects. The children were examined very closely for signs of infection in nose, throat and lymph nodes. The condition of the teeth also received close attention. The children's previous history of infection was checked.

In most cases of acute respiratory infections cultures were made from throat swabs. At the end of the semesters swab cultures were made from all children. On at least 6 occasions during the observation year AST and sedimentation reaction (SR) was determined for all children. AST was performed according to directions given by *Kalbak* and Todd's standard serum was used. SR was determined as described by *Westergren*. So-called micro-SR never was used. *Cultivation from throat swabs* was performed aerobically and anaerobically on 10 per cent horse blood agar. The presence on the plate of typical colonies in most cases was taken as proof of the diagnosis of hemolytic streptococci. In some doubtful cases, however, tests for soluble hemolysins were performed.

The Results.

The AST values obtained are shown in tab. 1, also giving the distribution among the age groups. The values are divided into two groups. *Infection values* were obtained from children, when apparently influenced by infection with hemolytic streptococci. Other values are named *health values*. For judging how long a

time after an infection an elevated titer can be considered as influenced by that infection, not only the clinical course and the type of the AST curve but also SR has played an important role. This time never has been less than two months. A remaining elevated SR has been thought to unveil a persistent influence of the infection.

Table 1.

610 values in 103 children

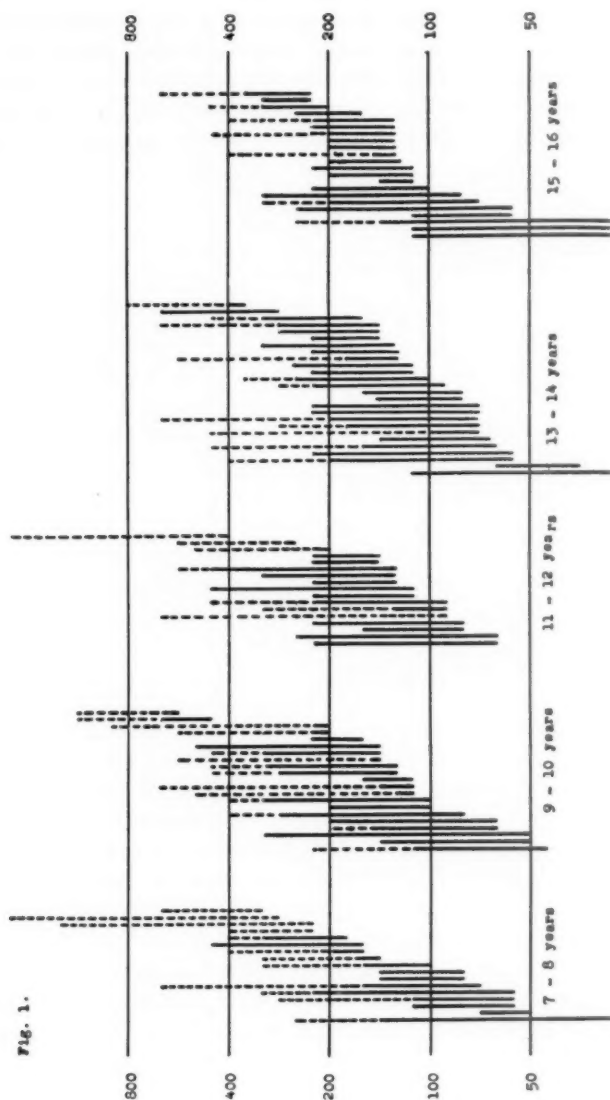
| Age, years | 7—8 | | 9—10 | | 11—12 | | 13—14 | | 15—16 | | Total | |
|-----------------------------|-----|----|------|----|-------|----|-------|----|-------|----|-------|-----|
| Number of children | 17 | | 21 | | 17 | | 26 | | 22 | | 103 | |
| AST | H | I | H | I | H | I | H | I | H | I | H | I |
| >800 | — | 3 | — | 5 | — | 1 | — | — | — | — | — | 9 |
| 401—800 | 1 | 18 | 2 | 25 | 2 | 12 | 4 | 11 | — | 5 | 9 | 71 |
| 201—400 | 5 | 19 | 17 | 14 | 21 | 12 | 24 | 9 | 26 | 5 | 93 | 59 |
| 101—200 | 27 | 2 | 46 | 1 | 41 | — | 73 | — | 74 | — | 261 | 3 |
| 51—100 | 24 | — | 11 | — | 11 | — | 27 | — | 12 | — | 85 | — |
| 25—50 | 1 | — | 1 | — | — | — | 8 | — | 10 | — | 20 | — |
| Total | 58 | 42 | 77 | 45 | 75 | 25 | 136 | 20 | 122 | 10 | 468 | 142 |
| Health values over 200 % | 10 | | 25 | | 31 | | 20 | | 21 | | 22 | |

H = «health values».

I = «infection values».

A more perspicuous picture of the AST values of different age groups is presented in the following graph (fig. 1) where each child is represented by a column. The continuous part of the column marks the range for the health values in the single case while the dotted part indicates the range of infection values. (Single infection values may fall within the range marked by the continuous part of the column.)

A glance at the graph gives certain information. Thus a considerable variation is present between high and low values, both between different children and between different values of the same child. These variations are most pronounced in the very youngest children.



AST in Children free from Clinical Infection with Hemolytic Streptococci.

Of 103 children only 52 after a very careful analysis could not be suspected during the whole year to be influenced by chronic or recent acute infections. The distribution of their AST values is seen in tab. 1 and fig. 1. As many as 30 of these children presented values over 200 at one or several occasions. As an AST value of 200 generally is considered to be the upper limit for the normal range of the reaction, this fact is remarkable. Another group of 21 children, shown to be influenced by infection with hemolytic streptococci for some period of the year, presented titres over 200 even on occasions when they were clinically free from such infection. The number of children with such unexplained high titres within the different age groups is given below.

Table 2.

| Age: | 7—8 | 9—10 | 11—12 | 13—14 | 15—16 | Total |
|---|-----|------|-------|-------|-------|-------|
| Number of children | 17 | 21 | 17 | 26 | 22 | 103 |
| Do with unexplained AST over 200 | 3 | 12 | 12 | 15 | 9 | 51 |

The high number of children presenting unexplained high titres is striking except for the youngest ones who have spent less than one year at the institution.

The Incidence of Infections with Hemolytic Streptococci in Different Age Groups.

In fig. 1 the high frequency of elevated values due to infections with hemolytic streptococci in the lowest age group is seen to diminish with the increase of age. A numerical expression of this fact is given below:

Table 3.

| Age: | 7—8 | 9—10 | 11—12 | 13—14 | 15—16 | Total |
|--|-----|------|-------|-------|-------|-------|
| Number of children | 17 | 21 | 17 | 26 | 22 | 103 |
| Do with infections followed by AST over 200 | 12 | 13 | 7 | 11 | 7 | 50 |
| Do per cent | 71 | 64 | 41 | 43 | 32 | 49 |

The dominating importance of hemolytic streptococci for the infections of school children appears from tab. 4, where all cases of acute respiratory infections are tabulated, which passed sufficiently isolated from previous and following infections to permit a judgement of their influence on AST. An established elevation of the titre has been considered to be present only when a doubling of the initial value occurred.

Table 4.

| Diagnosis | AST increased | | AST not increased | |
|---|---------------|-----|-------------------|-----|
| | HS+ | HS— | HS+ | HS— |
| Rhinitis | — | — | 1 | 9 |
| Bronchitis | 13 | 6 | 3 | 11 |
| Pharyngitis | | | | |
| Tonsillitis | 8 | — | — | — |
| Otitis media | 6 | — | — | — |
| Sinusitis maxillaris | 4 | — | — | — |
| Lymphadenit. colli sept. | 1 | — | — | 1 |
| Pleuritis exs. septica | 1 | — | — | — |
| Impetigo contagiosa | — | 1 | — | — |
| Erysipelas | 1 | — | — | — |
| Hepatitis epidemica | — | 1 | 1 | 7 |
| Morbilli without signs of complications | 3 | 4 | 2 | 11 |

HS = Hemolytic streptococci cultivated from throat swabs.

During the observation year an epidemic of infectious hepatitis occurred. The cases of this disease are presented in tab. 4 and do not offer anything of interest with regard to AST. More noteworthy, however, is the conduct of AST in some cases of measles. 22 children contracted the disease and only 2 presented clinically demonstrable complications (in both cases maxillar sinuitis). Of the 20 uncomplicated cases not less than 7 (i. e. 35 per cent) developed clear elevations of AST.

AST in Chronic Infections.

Of all the children, 16 presented signs of *chronic infectious processes in the throat and/or tonsilli* at repeated examinations.

In 8 of these also persistent enlarged lymph nodes were found. These children generally had AST and SR higher than the average. In acute exacerbations considerable elevations of AST and SR often occurred. This group is presented in tab. 5.

Particularly bad condition of teeth has been observed in several children but only 5 of those were free from signs of other co-existent chronic infections. These children presented either severe general and untreated caries or very many fillings, among them several root fillings. In tab. 5 this group of children is presented, cases with regional enlarged lymph nodes being divided from the others.

Table 5.

| Group | Enlarged regional lymph glands | Number of children with AST < 200 |
|--|--------------------------------|-----------------------------------|
| Chronic throat infection (15) . . | { present (8) | 8 |
| | { absent (8) | 6 |
| Bad condition of teeth (5) . . . | { present (3) | 3 |
| | { absent (2) | 0 |
| All children (103) | — | 80 |
| Children without clinical infection with hemolytic streptococci (52) | — | 30 |

Finally it was determined whether the presence of hemolytic streptococci in the throat is followed by a tendency for elevated AST. The result is given below. The analysis comprises the examination in december.

Table 6.

| Hemolytic streptococci in throat cultures | Signs of inflammatory reaction | Number of children with AST | |
|---|--------------------------------|-----------------------------|-------|
| | | ≤ 200 | > 200 |
| present (25) | present (16) | 3 | 13 |
| | absent (12) | 7 | 5 |
| absent (71) | present (14) | 2 | 12 |
| | absent (57) | 47 | 10 |

} = 64 p. c.
 } = 31 p. c.

Discussion.

Despite the difference in epidemiologic respect between children in an internate and other school children a group of the former type was chosen as the object of this study. Such a group can be very closely observed and the control is not interrupted, when the child falls ill, since the interne is not sent home, as other school children, but nursed within the school.

AST in Children free from Established Infection with Hemolytic Streptococci.

Previous investigations on the whole have indicated a tendency for higher AST values in children between the age of 6 and 10 than in adults of the same population. In the series now reported, however, children 7—8 years of age present fewer elevated AST in health than older children (tab. 1, 2 and fig. 1). Possibly the difference is explained by the high incidence of infections with hemolytic streptococci of the first year classes. This high incidence may have increased the possibility of including values influenced by such infections into previous »normal groups». The accurate registration of even slight and transitory upper respiratory infections and the extended observation time in this investigation had made possible to rule out most of the infection values.

The Incidence of HS Infections.

The disposition of the youngest children for infections is shown in tab. 3 where an even regression of the frequency of infection values parallel with the increase of age is evident. The figures represent the registered hemolytic streptococcus infections. Unexplained elevations of AST are, however, also frequent and thus we probably have to reckon with a high incidence of unregistered infections.

All cases of acute infections which were sufficiently isolated from previous and following infections to permit a distinguishing of their influence on AST are reported in tab. 4. The figures of the table must be taken as approximate, partly because the criterion of titer elevation is arbitrarily chosen, partly because the demonstration of hemolytic streptococci in the throat accord-

ing to usual routine is not very accurate. Nevertheless the table gives some information on the prominent importance of hemolytic streptococci among the pathogens of childhood.

Two epidemics of virus diseases also are reported in tab. 4. In the cases of epidemic hepatitis no subsequent elevations of AST occurred (the unspecific inhibition of hemolysis of icteric serum disregarded). On the other hand, 35 per cent of the clinically uncomplicated cases of measles presented clear elevations of AST. Thus it seems possible that an influence of a latent HS infection exists in many cases of measles which do not present any clinical signs of complication.

AST in Chronic Infections.

Chronic pharyngitis and tonsillitis, the symptoms of which often were slight, almost regularly were followed by elevated AST. This tendency was more pronounced when reactions of regional lymph nodes were present (tab. 5). A few children presented an especially bad condition of teeth, and in 3 of them regional lymphoid reactions were found together with hemolytic streptococci in the throat. These children had very high titres, while the other two who did not present enlarged lymph nodes and no hemolytic streptococci in the throat, had normal AST.

It is interesting that both types of chronic infection just mentioned had a more pronounced influence on AST when accompanied by regional lymph reactions than when lacking such reactions.

The Correlation between the Presence of Hemolytic Streptococci in the Throat and AST.

From tab. 6 it is apparent that the presence of hemolytic streptococci in throat cultures almost regularly was accompanied by an elevated AST when inflammatory reactions were present. The presence, however, of streptococci per se, without any reaction of the upper respiratory ducts, more often coexists with a normal AST in this group of children. On the other hand, many children with signs of respiratory infection and an elevated AST presented no hemolytic streptococci in the culture. This fact probably is to be seen as a sign of the inaccuracy of the method

of cultivation, as no enriching medium was used. 64 per cent of children with hemolytic streptococci in throat cultures presented an AST over 200 compared with 31 per cent of the children with negative cultures. *Packalén* in a study gives very similar figures, 73 resp. 32 per cent.

Summary.

103 children between 7 and 16 years of age have been clinically observed and followed up with AST for one year.

1. AST in health in children 7 and 8 years of age generally was low. In older children AST was adjusted to a higher level unaltered up to the age of 16 years.

2. Even very slight respiratory infections, likely to escape observation, often were followed by elevated AST persistant for a long time. Such elevations were most common in the youngest children.

3. Chronic infections of the respiratory tract often were followed by elevated AST, especially when accompanied by regional lymphoid reactions.

4. The presence of hemolytic streptococci in the throat regularly influenced AST only when inflammatory reactions existed.

5. According to these facts AST in school children should be very carefully evaluated as a sign of actual hemolytic streptococci infection.

Finally, measles, even when apparently uncomplicated, often was followed by an elevation of AST.

Résumé.

103 enfants entre 7 et 16 ans ont été observés cliniquement et suivis avec AST pendant une année.

1. Dans la santé chez des enfants de l'âge de 7—8 ans AST était généralement bas. Chez des enfants plus âgés AST était ajusté à un niveau plus haut inchangé jusqu'à l'âge de 16 ans.

2. Même des infections respiratoires très légères et pouvant échapper à l'observation ont été suivies d'un AST élevé et persistant longtemps. De telles élévations étaient plus fréquentes chez les plus jeunes enfants.

3. Des infections chroniques de l'appareil respiratoire étaient souvent suivies d'un AST élevé, spécialement quand elles étaient accompagnées de réactions lymphoïdes régionales.

4. La présence de streptocoques hémolytiques dans la gorge n'influçait l'AST que quand il y avait des réactions inflammatoires.

5. D'après ces faits l'AST chez les écoliers devrait être évalué avec soin comme le signe d'une vraie infection de streptocoques hémolytiques.

Finalement, la rougeole, même quand elle était apparemment sans complications, était souvent suivie d'une élévation de l'AST.

Zusammenfassung.

103 Kinder im Alter von 7—16 Jahren wurden klinisch beobachtet und ihr AST ein Jahr lang kontrolliert.

1. Bei gesunden Kindern im Alter von 7—8 Jahren war der AST allgemein niedrig. Bei älteren Kindern lag der AST bis zu 16 Jahren unverändert höher.

2. Auch ganz geringfügige Infektionen der Atemwege, die der Beobachtung leicht entgehen können, hatten oft einen erhöhten AST zur Folge, der lange Zeit bestehen blieb. Eine solche Erhöhung kam am häufigsten bei den jüngsten Kindern vor.

3. Nach chronischen Infektionen des Respirationstraktes war der AST oft erhöht, besonders wenn sie von Reaktionen der regionären Lymphdrüsen begleitet waren.

4. Die Anwesenheit haemolytischer Streptokokken im Rachen beeinflusste den AST regelmässig nur, wenn entzündliche Reaktionen vorhanden waren.

5. Gemäss dieser Tatsachen sollte der AST bei Schulkindern als Kennzeichen einer bestehenden haemolytischen Streptokokkeninfektion sorgfältig beachtet werden.

Schliesslich hatten Masern, auch wenn sie keine Komplikationen zeigten, oft eine Erhöhung des AST zur Folge.

Resumen.

103 niños de 7 a 16 años fueron observados clínicamente y tratados con AST durante un año.

1) En los niños sanos de 7 a 8 años de edad, AST fué generalmente muy bajo. En niños de mayor edad AST quedó a un nivel más alto, el cual no sufrió modificación hasta la edad de 16 años.

2) Las infecciones respiratorias, aun las muy ligeras, fáciles de escapar a una observación, fueron muchas veces seguidas por un alto AST persistente durante bastante tiempo. Estas alzas fueron muy comunes especialmente entre los niños más jóvenes.

3) Las infecciones crónicas del tracto respiratorio fueron muchas veces seguidas de un alto AST, especialmente si iban acompañadas de reacciones linfóideas regionales.

4) La presencia de estreptococos hemolíticos en la garganta influyó regularmente sobre AST sólo en el caso de haber reacciones inflamatorias.

5) De acuerdo con lo anterior se debería considerar el AST en niños escolares como una señal de infección efectiva de estreptococos hemolíticos.

El sarampión, aun cuando aparentemente no presentaba complicaciones, fué seguido muchas veces por un aumento de AST.

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FROM THE MUNICIPAL BACTERIOLOGICAL CENTRAL LABORATORY,
STOCKHOLM. (CHIEF: PROF. H. DAVIDE).

Antistaphylolysin Titre in School Children.

By

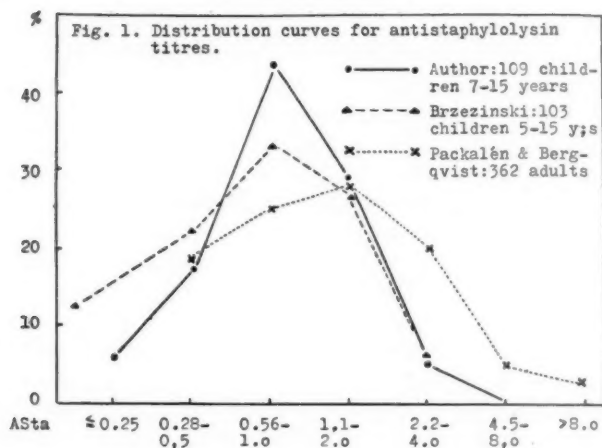
GÖSTA TUNEVALL.

In a previous paper (6) the author has reported on antistreptolysin titres in a group of school children, closely followed up for one year. The following report deals with the same group of children, the character of which can be seen in the above mentioned paper.

The pathogenic significance of the staphylococci and especially *Staphylococcus aureus* has been more and more recognized in recent years. In children the staphylococci must be considered as very often provoking or contributing to infectious conditions of various kinds. For the immunological study of staphylococcal infections the antistaphylolysin reaction (ASta) has been found to be well suited. The antistaphylolysin titre in normal and pathological groups has been investigated by several authors but only few of them have considered the conditions in children. So BATES and WEISS (1), BRYCE and BURNET (2) and BRZEZINSKI (3) have found considerably lower titres in children than in adults. The correlation between antistaphylolysin titre and the findings in nose and throat cultures of *staphylococcus aureus* as well as the staphylococcal carrier rate has been studied by PACKALÉN and BERGQVIST (5).

Author's investigations.

The investigated group consisted of 109 children 7 to 16 years of age, clinically followed up for one year. At the end of the year two determinations of ASta were made with an interval of 8 weeks. At the same time the presence of *Staphylococcus aureus*

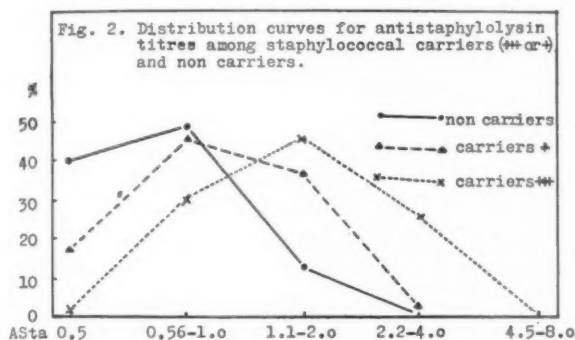


in throat cultures was recorded. According to PACKALÉN and BERGQVIST (5) the staphylococcal findings in the throat reflect fairly accurately the corresponding flora in the nose. The classification of the staphylococci as belonging to the aureus group was done by observing their pigment formation on horse blood agar after 24 hours at 37° C. and an additional 24 hours at room temperature. The pigment formation also was taken as a sign of pathogenicity, as the parallellism between the formation of staphylolysin, coagulase and pigment is found by the same authors to be very close. Determinations of the antistaphylolysin titre was carried out chiefly by the technique described by IPSEN (4), as modified by PACKALÉN and BERGQVIST (5). The higher of the two titres from each child was recorded as the ASTa value.

The distribution of the antistaphylolysin titres.

The ASTa values of the 109 children, all clinically free from staphylococcal infection, are shown in Fig. 1.

The figure shows a sharp maximum for the titres between 0.56 and 1.0, however, the group 1.1 to 2.0 is also large. These two groups together comprise 72 % of the children. Titres over



2.0 are infrequent. For comparison the distribution of the ASTa values in BRZEZINSKI's (3) age group 5—15 years is shown in the figure and it is seen to correspond fairly well to that of the author's material. However, PACKALÉN and BERGQVIST (5) found somewhat higher values in a group of Swedish adults who were mostly tubercular patients. These results are also represented in the figure.

Antistaphylolysin titres in relation to staphylococcal findings in the throat cultures.

Of the 109 children, 40 were free from pathogenic staphylococci in the throat cultures (36 %), in 49 children less than 5 % of the flora, as recovered in the cultures, consisted of staphylococci (36 %) and in 20 children the findings of staphylococci were more abundant (19 %). The distribution of the ASTa values within these three groups is shown in Fig. 2.

The parallellism between the ASTa values and the staphylococcal findings in the throat cultures, previously demonstrated by PACKALÉN and BERGQVIST (5), is easily visible even in this material.

The Coincidence of staphylococcal and streptococcal infections.

As mentioned before the children in this investigation were followed even with determinations of the antistreptolysin titre.

It is noteworthy that 25 % of the children with ASta values over 1.0 presented antistreptolysin titres over 400, while only 9 % of the children with lower ASta values exceeded this antistreptolysin titre.

Summary.

109 children 7 to 16 years of age, all free from clinically manifested staphylococcal infection, were examined for the presence of pathogenic staphylococci in the throat and their antistaphylo-lysin titre was determined. 63 % of the children were found to be carriers of staphylococci. 72 % of them had ASta values between 0.56 and 2.0 international units per ml, 23 % had lower values and only 5 % had higher values. The frequency of high ASta values was considerably larger in the carrier group than in the non-carriers. A certain tendency to coincidence of staphylococcal and streptococcal infections was demonstrated by the fact that high antistreptolysin titres were more common among children with ASta values over 1.0 than in those not exceeding that level (25 viz. 9 %).

Résumé.

109 enfants âgés de 7 à 16 ans, tous exempts d'infection par staphylocoques manifestée cliniquement, ont été examinés pour déterminer la présence de staphylocoques pathogènes dans la gorge et leur titre d'antistaphylo-lysin fut déterminé. 63 % des enfants ont été trouvés porteurs de staphylocoques. 72 % d'entre eux avaient des valeurs ASta de 0.56 à 2.0 unité internationale par ml, 23 % avaient des valeurs moindres et seulement 5 % avaient des valeurs supérieures. La fréquence de valeurs élevées d'ASta était considérablement plus grande chez le groupe des porteurs que chez les non-porteurs. Une certaine tendance à une coincidence d'infections par staphylocoques et une infection par streptocoques fut démontrée par le fait que de hauts titres d'antistreptolysin était plus fréquents chez les enfants ayant des valeurs d'ASta surpassant 1.0 que chez ceux ayant des valeurs n'excédant pas ce niveau (25 viz. 9 %).

Zusammenfassung.

109 Kinder im Alter von 7—16 Jahren, vollständig frei von einer klinisch manifesten Staphylokokken-Infektion, wurden auf die Anwesenheit pathogener Staphylokokken im Rachen untersucht und ihr Antistaphylolysin-Titer festgestellt. 63 % der Kinder waren Staphylokokkenträger. 72 % von ihnen hatten AS_ta-Werte zwischen 0.56 und 2.0 internationalen Einheiten per ml, 23 % hatten niedrigere und nur 5 % höhere Werte. Die Frequenz der hohen AS_ta-Werte war in der Gruppe der Bazillenträger beträchtlich grösser als bei den Nicht-Trägern. Eine sichere Tendenz für das Zusammentreffen von Staphylo- und Streptokokken-Infektionen wurde durch die Tatsache dargelegt, dass hohe Antistreptolysintiter bei Kindern mit AS_ta-Werten über 1.0 häufiger waren als bei denen, die diese Grenze nicht erreichten (25 gegen 9 %).

Resumen.

109 niños de 7 a 16 años de edad, todos libres de estafilococia, fueron examinados para averiguar la presencia de estafilococos patógenos en la garganta, determinándose el título de antiestafilolisina. Se halló que el 63 % eran portadores de estafilococos. El 72 % tenían valores AS_ta entre 0.56 y 2.0 unidades internacionales por milímetro, el 23 % valores menores y sólo el 5 % valores más altos. La frecuencia de altos valores AS_ta era considerablemente mayor en el grupo portador que en el otro. Se comprobó cierta coincidencia de estafilococia y estreptococia, ya que los títulos altos de antiestreptosina eran más comunes entre los niños con valores AS_ta de más de 1.0 que entre aquéllos cuyos valores sobrepasaban este nivel (25.0 sea el 9 %).

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(FROM BORÅS HOSPITAL, PEDIATRIC DEPT. HEAD: B. SÖDERLING, M. D.)

The Initial Loss in Weight of Prematurely Born Infants and their Weight During the First Two Years of Life.

By

KJELL L. MÖLLER.

According to RUSCH (4) the initial loss in weight of newborns during the first few days of life is on an average 7.31 per cent of the birth weight. GYLLENSWÄRD (2), who studied newborns with a birth weight exceeding 2 200 g, estimates the initial loss in weight to be 6.21 per cent \pm 0.07. The smaller the birth weight was, the smaller was the loss per cent.

Opinions differ concerning the initial loss in weight of prematurely born infants. Some authors consider the loss to be proportionally larger than in full-term infants, possibly proportional to a relatively larger body surface, whilst others (RUSCH (4) et al.) contend that premature children lose less weight, the loss decreasing with diminishing birth weight.

Material.

The examination material comprised those infants weighing less than 2 500 g at birth and nursed from 1939 to the end of 1945 at the Pediatric Dept. of Borås Hospital, and released as healthy. Infants with substantial delivery lesions and grave deformations have not been included in this material. On account of its heterogeneous composition, another group consisting of 20 infants with a birth weight below 1 500 g was not included either in the following calculation (birth weights between 900 and 1 460 g). The remaining material consists of 298 infants weighing between 1 500 and 2 499 g at birth. The nourishment, consisting in almost

all cases initially of breast milk, was commenced 6 hours after birth and as a rule only six meals were given per day. The initial quantity of milk, which was 5 cc. per meal, was increased by 5 cc. per meal per day until the meal had increased to what was considered a suitable quantity. In addition to these meals some infants showing signs of dehydration were given fluids subcutaneously once or more often during the first few days of life. No extra fluid was administered per os. Neither was any additional nourishment such as amino acids with glucose or the like given before the infant had ceased losing weight.

Results.

The initial loss per cent of the birth weight of the 298 infants amounted to 8.40 per cent \pm 0.13. Compared with the number obtained by GYLLENSWÄRD this decrease is 2.39 per cent \pm 0.15 greater.

As will be apparent from the table below, the material has been divided into groups according to birth weight. The prematurity is calculated on the basis of the date of the last menstruation as stated by the mother and on the presumption that 280 days is the normal duration of pregnancy.

| Birth weight g | No. of infants | Prematurity. Days | Initial loss in weight. Per cent |
|-------------------|-------------------|----------------------|-------------------------------------|
| 1500—1699 | 30 | 47.9 | 9.01 \pm 0.68 |
| 1700—1899 | 48 | 33.8 | 9.15 \pm 0.62 |
| 1900—2099 | 63 | 34.2 | 8.44 \pm 0.40 |
| 2100—2299 | 86 | 29.9 | 7.93 \pm 0.66 |
| 2300—2499 | 71 | 24.3 | 8.00 \pm 0.32 |

No statistically significant difference in the initial loss in weight between the various weight — groups can be shown.

The material comprises 78, or 26.2 per cent, twins with an average birth weight of 2 031 g. With a prematurity of 33.9 days and an initial loss in weight of 8.66 per cent \pm 0.38 they do not differ from the other infants with the same average birth weight.

In the lowest weight-group ten of the children had been given fluid subcutaneously; the other 20 exhibited an initial loss in weight

of 8.27 per cent. In the highest weight — group fluid was administered subcutaneously to 11 infants; the other 60 lost 8.05 per cent weight. Neither in the other classes could any substantial difference in the initial loss of weight be determined between those infants who were given fluid parenterally and those who were not. Information concerning the duration of pregnancy was available in 263 cases. These have been divided into two groups, one with a loss in weight of ≥ 8.4 per cent and one with a loss of < 8.4 per cent.

| Loss in weight. Per cent | No. of infants | Prematurity. Days | Birth weight. Average, g |
|-----------------------------|-------------------|----------------------|-----------------------------|
| 11.14 ± 0.20 | 110 | 37.9 ± 1.7 | 2089 |
| 6.02 ± 0.15 | 153 | 26.7 ± 1.4 | 2086 |
| Difference: 5.12 ± 0.25 | | 11.2 ± 2.2 | |

The group with a higher initial loss in weight thus shows a statistically significant greater prematurity. The average birth weight is the same in both cases. It is obvious that the degree of the initial loss in weight does not depend so much on the relatively greater or smaller birth weight of the premature infant. A large initial loss in weight is rather a sign of greater immaturity.

Increase in weight during the first two years of life.

The physical development of premature infants during the first few years of life has been studied by many investigators. During his studies YLPPÖ (7) found that as far as physical development is concerned a child with a birth weight lower than 2 500 g does not begin to approach a full-term child before the third to fifth year of life. In cases with a very low birth weight this developmental deficiency still exists in the 7th and 9th year of life. von SYDOW (5) has studied a Swedish material consisting of premature children who even in their 10—11th year were not so heavy as full-term controls. Also ILLINGWORTH (3) was able to show that premature infants have a relatively smaller weight during childhood. Those children who had been given suck more than six months had developed better than those who had received mother's milk less than 2 months.

Material.

Of the 298 cases of prematurely born infants 126 were controlled at the Children's Welfare Centres of Borås 6 months or longer subsequent to release from hospital. Owing to the removal of some of the families from town and for other reasons for release, this number dwindled considerably, so that of the 126 infants, at the age of one year, 112 were still on the control register, and 95 at the age of two.

Results.

The weights at 6 months, 1 year and 2 years were distributed among the various weight-groups as follows.

| Birth weight | Weight at 6 mnths. | Weight at 1 yr. | Weight at 2 yrs. |
|--------------|--------------------|-----------------|------------------|
| 1500—1699 | 5821 [n=8] | 8614 [n=8] | 9459 [n=8] |
| 1700—1899 | 6199 [n=20] | 8737 [n=20] | 11208 [n=19] |
| 1900—2099 | 6592 [n=26] | 9442 [n=24] | 11938 [n=19] |
| 2100—2299 | 6736 [n=38] | 9427 [n=38] | 12094 [n=31] |
| 2300—2499 | 6950 [n=29] | 9522 [n=22] | 12141 [n=18] |

According to von SYDOW (6) the weight of healthy Swedish baby boys with a birth weight of 3.5—4 kg at the age of 176—195 days is 7 910 g (6 460—9 360), and of girls with a birth weight of 3—3.5 kg it is calculated to be 7 210 g (6 010—8 410). At the age of 356—375 days boys weigh 10 340 g (8 450—12 230) and girls, 9640 g (8 080—11 200). According to BROMAN, DAHLBERG, and LICHTENSTEIN (1) two year-old Swedish boys weigh 10.7—15.2 kg (average 12.9), and girls, 10.4—14.9 (average 12.6). The material of the present study thus shows a favourable increase in weight when compared with those figures. The examined premature material with a birth weight exceeding 1 500 g, is selected in so far as it consisted entirely of town children who can be carefully observed by the nurses and doctors at the Children's Welfare Centres.

Of the infants 55 had been nourished entirely or partly on breast milk for six months and longer. These children have been compared with the 71 infants weaned before this age.

| | Birth weight | Weight at 6 months | Weight at 1 year | Weight at 2 years |
|----------------------|-----------------|-----------------------|---------------------|----------------------|
| Breast-fed | 2296 | 6643 \pm 125 | 9247 \pm 147 | 11880 \pm 181 |
| Non-breast-fed | 2083 | 6616 \pm 83 | 9278 \pm 118 | 11731 \pm 170 |

The handicap in weight registrable in infants brought up on breast milk is thus eliminated by the age of six months, after which the rate of increase in weight is equal in both groups.

The subsequent development in weight of the 52 children who experienced an initial loss of ≥ 8.4 per cent has been compared with that of those 74 showing an initial loss of < 8.4 per cent. No statistically significant difference in the weights of the two groups could be established for any of the three ages: 1/2, 1, and 2 years.

Summary.

The initial loss in weight in 298 infants with a birth weight of 1500—2499 g was 8.4 per cent. The loss in weight was not connected with the birth weight but with the degree of praematurity.

The increase in weight during the first two years of carefully supervised praemature children was very satisfactory. Infants fed on unnatural food or with a high initial loss in weight were not inferior to the others.

Résumé.

Chez 298 enfants dont le poids à la naissance variait de 1500 à 2499 gr la perte initiale de poids était de 8,4 %. La perte initiale de poids ne dépend pas du poids à la naissance mais du degré de prématurité. Chez des enfants prématurés, minutieusement suivis on a constaté, pendant les deux premières années, une augmentation de poids très satisfaisante. Les enfants non nourris au sein ou ayant eu une forte perte initiale de poids, n'étaient pas inférieurs aux autres.

Zusammenfassung.

Eine Gewichtskontrolle der in der Kinderwohlfahtszentrale Borås beobachteten Frühgeburten im Alter von 6 Monaten, 1

Jahr und 2 Jahren ergab weder einen Unterschied zwischen den mit Muttermilch und den künstlich ernährten Kindern noch zwischen mit solchen hohem und niedrigem Initialverlust.

Resumen.

La pérdida inicial de peso registrada en 298 niños, con un peso de nacimiento de 1500 a 2499 gramos, fué de un 8,4 por ciento. La pérdida de peso no guardaba relación con el peso de nacimiento, sino con el peso prematuro.

El aumento de peso durante los dos primeros años en niños prematuros cuidadosamente controlados fué muy satisfactorio. En los niños criados con alimentos artificiales y en los niños con gran pérdida inicial de peso no se pudo apreciar ninguna diferencia de peso en comparación con los otros.

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FROM THE SACHS'S CHILDREN'S HOSPITAL, STOCKHOLM (HEAD: DOC.
J. H. MAGNUSSON).

Two Cases of Congenital Malformations after Exposure to Measles in Early Pregnancy of Already Immune Mothers.

By

ANDERS HAGSTRÖMER.

In 1941 Gregg published in Australia a number of cases of congenital malformations in infants whose mothers had suffered in early pregnancy from an exanthematous disease diagnosed as rubella. Since then, some hundreds of similar cases have been described in different countries. Ten cases have been reported in the Scandinavian countries (1, 2, 3, 4, 9).

Attempts have been made to discover whether other virus infections can injure the embryo in a similar way (5, 6, 7). No such causal relationship has as yet been established, but the future may hold many surprises in this field.

The malformations following maternal rubella have often been multiple and shown a definite pattern, i. e. deaf-mutism, cataract, heart disease (among others patent ductus arteriosus and/or patent foramen ovale) and mental deficiency. Multiple abnormalities of this type compose the prenatal rubella syndrome. This syndrome (congenital cataracts and congenital heart defects) has been described as occurring in an infant, whose mother was unaware of illness when pregnant (8).

Two other children belonging to the same mother had, however, had rubella during the second month of the mother's pregnancy. It may be assumed that the rubella virus had been forwarded within the mother without her being ill herself.

Within a short period of time the author has observed two cases of a different type of congenital malformations, i. e. harelip

and cleft palate, in children whose siblings had measles during the first stage of the mother's pregnancy.

Case 1.

Boy child H. P. J., born at the South Maternity Hospital August 7, 1947 (journal 2021/47). Head presentation. Placenta no comment. Birth weight 3 580 g. Length 50 cm.

Left-sided hare-lip and partial cleft palate (cheilo-palato-schisis) were the only visible defects. Similar or other defects are unknown among the nearest relatives. (A half second-cousin ? is said to have some type of lip-palate defect.) The boy's parents were healthy, had been married since 1939 and were not related to each other. The boy's father, a tombstone engraver by profession, was 30 years old at the time of the child's birth. The mother was 25 and had not had work outside the home since 1945. She had undergone three former pregnancies:

1. 1939 a well-shaped baby girl was born. Weight 3 400 g.
2. 1941 a well-shaped boy. Weight 3 700 g.
3. 1944 miscarriage in the third month.

As to the actual pregnancy, she reports the following: The last normal menstruation began October 9, 1946. She was bothered by slight to moderate nausea and slight vomiting, mostly mornings, from the middle of the second through the third month. Appetite was normal. No loss of weight. During the three former pregnancies, her discomforts had been of the same type and degree as this time. They had begun at about the same stage of pregnancy. During the last gestation at the end of the third month during the Christmas holidays, the mother had had a slightly running nose and a cough. Otherwise she had been healthy the entire time.

On the other hand, a brother of the child had had measles during the latter half of the mother's second month of pregnancy. Measles were prevalent among other families in the same apartment house. November 14th, the brother showed signs of fatigue and had a running nose. The following day, he "coughed badly", shunned light and had as high as 39° C fever. In the evening, an eruption broke out on his face and spread over the entire body though mostly on the chest and abdomen. The fever decreased after 2—3 days. At the same time, the eruption began to fade and had disappeared by the end of 5—6 days. (The sister who had had measles on an earlier occasion when visiting friends alone in the country, was not taken ill during November—December 1946.) The mother herself had had measles, according to report, in 1930 at 8—9 years of age.

Case 2.

Boy child J.-E. M., born at the South Side Hospital November 16, 1947 (journal 4428/47). Head presentation. Placenta no comment. Birthweight 4 100 g. Length 52 cm.

Only visible defects were cleavage of the back palate, a rudimentary right ear placed a good distance forward on the cheek and a notably small chin. The thorax was possibly somewhat arched. Similar or other defects are unknown in the family.

The boy's parents were healthy. They had been married since December 1945 and were not related to each other. The child's father, a grinder by profession, was 27 years old at the time of the child's birth. The mother was 24 and had not worked outside the home since 1946. Both parents are Estonian refugees. The mother had been pregnant only once before. In July 1946, she gave birth to a well-shaped girl. Weight 4 200 g.

The mother reports the following as to the actual pregnancy: The last menstruation began February 3, 1947. During the second (?) month of pregnancy, she was bothered several times by slight attacks of nausea. She never vomited. Her appetite was good the entire time. Probably no loss of weight.

The family lived in cramped quarters and under nervous conditions. The mother was as little troubled by her former pregnancy as by this one. Except for a slightly running nose during the last pregnancy week, she was completely healthy the entire time.

On the other hand, *two cases of measles occurred in the family during the second month of pregnancy.* The mother's brother fell sick with measles about March 8th. March 20th, the mother's first child was taken ill with running nose, conjunctivitis, cough and fever between 39° and 40° C for approximately two days. At the same time, she had a large-spotted eruption which faded and disappeared after about one week. The doctor summoned, diagnosed measles. The mother herself had had measles, according to report, before 10 years of age.

Whether or not a causal relationship has existed between the siblings' measles and the malformations described, must be left unsaid. It seems, however, worth while bearing this possibility in mind.

In the related cases, exposure to measles occurred during the second month of pregnancy, i. e. in that stage of pregnancy, when fetal tissue is probably most prone to virus injury.

Summary.

A report is given of two cases of congenital malformations in infants, whose siblings had suffered from measles during the second month of their mothers' pregnancy. The mothers, them-

selves, were not affected by measles at this time but had had the disease in childhood.

The malformations in question were in one case cheilo-palato-schisis and in the other palato-schisis, micrognathy and a rudimentary ear.

It seems worth while bearing in mind a possible causal relationship between prenatal exposure to measles and congenital malformations.

Résumé.

Deux cas de malformations congénitales chez des enfants, dont les frères et sœurs avaient eu la rougeole pendant le deuxième mois de la grossesse de leur mère. Les mères elles-mêmes n'étaient pas atteintes de la rougeole à ce moment-là, mais elles l'avaient eue dans leur enfance.

Les malformations en question étaient dans un cas: «cheilo-palatoschisis» et dans l'autre: «palatoschisis», micrognathie et une oreille rudimentaire.

Il semble bon de se rappeler la possibilité d'une relation causale entre une exposition prénatale à la rougeole et les malformations congénitales.

Zusammenfassung.

Bericht über 2 Fälle von kongenitalen Missbildungen bei Kindern, deren Geschwister während des 2. Schwangerschaftsmonates der Mütter an Masern erkrankt waren. Die Mütter selbst wurden zu diesem Zeitpunkt nicht von Masern affiziert, sondern hatten diese Krankheit früher durchgemacht. Die erwähnten Missbildungen waren in einem Fall eine Cheilo-palatoschisis, in dem anderen eine Palato-schisis, Mikrognathie und ein rudimentäres Ohr.

Es scheint begründet, an die Möglichkeit eines kausalen Zusammenhanges zu denken zwischen dem Umstand, dass die Kinder pränatal einer Maserninfektion ausgesetzt waren und dem Auftreten der Missbildungen.

Resumen.

Se informa sobre 2 casos de malformaciones congénitas en niños cuyos hermanos primogénitos habían tenido sarampión durante el segundo mes de embarazo. Las madres no fueron afectadas por el sarampión, pero lo habían tenido durante la infancia.

Las malformaciones en cuestión eran queilopalatosquisis en un caso y en el otro palatosquisis, micrognatos y una orofaringe rudimentaria.

Parece que se debe tener presente un posible parentesco causal entre la exposición prenatal a sarampión y las malformaciones congénitas.

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FROM THE SAMARITEN CHILDREN'S HOSPITAL, STOCKHOLM.
(HEAD: PROF. N. MALMBERG.)

Congenital Varices of the Esophagus.

By

SIBVARD JORUP.

Esophageal varices may be due to many different causes. The commonest is stasis in the portal system, with a compensatory extension of the network of veins in the upper part of the stomach and the lower part of the esophagus, where the submucous plexus, in particular, may form powerful varices. Anastomoses over the hemorrhoidal plexuses and the mesenteric veins are rarely found, and even more rare are connections over the cutaneous veins on the abdomen, thorax and throat. The commonest cause of stasis in the portal system is cirrhosis of the liver; in this disease rupture of an esophageal varix is the immediate cause of death in approximately one in every ten cases, according to Eppinger. Other diseases of the liver in children, such as syphilis, may also give the same symptoms. Another cause is a direct blocking of the portal vein or the vena lienalis. This obstruction may be produced by a thrombus in the blood vessel, by changes in the parts adjoining the vessel which cause compression, or by changes in the vessel wall itself, such as occur in appendicitis complicated with peritonitis, pancreatitis, sepsis, syphilis, and so on, as the result of which a secondary thrombosis arises. Congenital anomalies causing stenosis have been described in a few cases. Cardiac disease with incompensation and chronic stasis in the portal system may also be complicated by esophageal varices. Varices and hemorrhage may develop when there are purely local changes in the veins of the esophagus. A local congenital weakness in the vessel wall, such as is seen in varices of the leg may, perhaps, also be a contributory factor.

In addition to these we have congenital varices, to which I will return further on.

When once esophageal varices have developed hemorrhage can sooner or later occur. This bleeding is usually the first sign of the underlying illness and shows a strong tendency to recur. The bleeding often causes secondary anemia. In addition to the more or less severe stasis, which can increase during defecation or miction, the bleeding is caused by a purely mechanical effect due to hard and badly chewed food, to rapid eating and large bites, arrosion by repeating gastric juice, local phlebitis or phlebosclerosis, or the development of necrosis as the result of deteriorating nutrition. We have on several occasions observed that the hemorrhages often occur in connection with an upper respiratory tract infection. The negative pressure in the thorax, and consequently also in the esophagus, causes the bleedings to be protracted and often copious. Splenomegaly, due to stasis, is another feature of the condition in most cases. In stenosis of the vena lienalis, as Wallgren has especially pointed out, this enlargement of the spleen is marked, and it subsides or disappears as the result of the decrease in tension brought about by rupture of an esophageal varix, the normal size of the spleen being regained after the lapse of one to two weeks. Opitz, among others, has studied these variations in the volume of the spleen, which may be regarded as pathognomonic of stasis of the vena lienalis. Ascites is a not uncommon finding in stenosis in the portal system, especially when the obstruction is centrally situated, whereas in the case of stenosis of the vena lienalis, if ascites occurs, it is less pronounced and is often transient.

Congenital varices of the esophagus are very rare, and are often associated with other deformities. Nochimowski found 8 cases which he described as congenital, when going through the literature in 1932. In addition to these he had 2 cases of his own. When describing these 10 cases he mentioned that nothing to account for the varices had been found, but he did not discuss the size of the spleen, for instance, which indicates whether there is stasis in the vena lienalis or in the portal system.

The first cases to be described are those reported by Roki-

tansky, in 1833 and 1856, patients of 44 and 24 years, respectively. They are so inadequately described that it is impossible to decide whether it was really a question of congenital abnormalities or not. In the first case, in which hematemesis had occurred at intervals over a period of two years, he mentioned that after each bleeding there was hydropic swelling. There is no mention of the heart, nor of the spleen.

Eberth, in 1880, described a case in which the patient, a man 40 years old, was suspected of having had typhus. He died of hemorrhage from esophageal varices, and at the postmortem examination a rather large, firm spleen was found.

Bristow's case, reported in 1859, was that of a 48 year old woman with an enlarged spleen and ascites.

In 1894, Friedrich had a case, a girl of 6, whom he observed for about two years. The spleen is not mentioned in the case history, but in the notes from the autopsy it is stated that the spleen was greatly enlarged. There was fatty degeneration in the liver, spleen, and kidneys. In addition, there were 400 cc. of milky fluid in the abdomen (fat content, 0.54 per cent). There was nothing remarkable found in the portal vein, the thoracic duct, or the vena azygos. The only positive finding was the esophageal varices.

Muller reported varices in a man of 43, and considered the cause to be alcoholism. Fatty degeneration was present but no cirrhosis of the liver. Varices were observed both above the cardia and below the pharynx. The spleen is not mentioned.

Jolasse had a case of an 11 year old boy with portal stenosis.

Vorpahl describes a case in which a newborn infant died of hemorrhage on the third day of life. The portal vein and liver were normal. The veins in general were situated close under the epithelium in the esophagus, in some places so closely packed together that they resembled a hemangioma under the microscope. This case is considered by Vorpahl to prove the correctness of the previous assumption that congenital esophageal varices really do occur.

Nochimowski's first case was a 32 year old workman who had sustained several gunshot wounds 10 years previously, some

of them on the right side of the thorax. He died of severe hematemesis, and at autopsy he was found to have a moderately large spleen (275 g.) indicating that during life it had been not inconsiderably enlarged and that there must have been stasis in the region of the portal vein and spleen even though the examiner had observed nothing abnormal there. The cause may well have been the wounds he had previously sustained. Wallgren has pointed out the difficulty of finding changes in the portal vein and vena lienalis at a postmortem examination conducted in the customary manner. Nochimowski's second case was that of a 64 year old workman. He died after a couple of copious bleedings, and at autopsy a small almost shrunken spleen was found. The liver and spleen were normal to the naked eye. No microscopical examination is described in the report. There was no ascites. The patient was cachectic. Nine years before, he had had an accident with electric current. Cases in which an interval of many years elapsed between the attacks of hematemesis are, it is true, on record, but a first attack at the age of over 60 points away from the possibility that the varices were congenital. The cause may perhaps have been the injury from the electric current sustained nine years previously.

Friedman described a case in 1934, a child of $3\frac{1}{2}$ years old who had thrown up bloody vomit on repeated occasions during the preceding 18 months. It was admitted to the hospital because of the bleeding, and physical examination revealed a distended abdomen with an enlarged spleen, the latter condition being especially noticeable on percussion. A few days later the child had another hematemesis and died in connection with it. Autopsy revealed the presence of varices but the spleen was not enlarged. Some obstruction was probably present but was not detected. This author states his case to be the eleventh congenital case.

Schatzki, in 1940, described 116 cases of varices of the esophagus. He mentioned that he had seen cases where liver and spleen were not palpated and no ascites was present. He does not, however, designate these cases as congenital, but in suspicious cases he has interpreted the roentgenogram of the varices

as probable cirrhosis of the liver. On the other hand, in a paper published in collaboration with Holmes in 1935, he mentions a case which he considered to be congenital. No details are given. He found esophageal varices in connection with cirrhosis of the liver in 50 per cent of the cases.

Hansson published a paper in 1944 describing three cases, the first patient, like ours, having had vomiting, sometimes streaked with blood, after his arrival home from the maternity hospital. He spent periods at the hospital, at 3 and 6 months of age, because of hematemesis. No enlargement of the spleen or other signs of portal stasis were observed. According to a personal communication from this author, the child now shows normal development, does not suffer from bleeding but has a tendency to vomit. Roentgenograms of the esophagus show a nearly normal picture; possibly it appears to be a little wider than is usual, and there are a couple of varix-like rarefied areas.

To these cases I now add a case treated at the Samaritan Children's Hospital.

Case Report. A Finnish boy, aged 6 months when admitted. The mother had had hemorrhages in the 5th to 6th months of her pregnancy, as the result of trauma. The remainder of the pregnancy and the delivery were normal. The boy's twin sister sucked well from the first, and has always been healthy. But the boy, our patient, refused the breast, and took very little nourishment. He vomited from the very first day, and after 2 or 3 months the vomit showed brownish discoloration. He vomited up, here, about 100 grams a day, the amount decreasing slightly after the institution of Skopyl treatment. The vomit was sometimes streaked with light red blood. On these occasions the boy was restless and irritated for half to one day, threw himself about and refused his food. After these attacks the hematemesis occurred; the amount vomited was never very much, at the most a couple of tablespoonsful of light-red or brownish vomit. The vomiting sometimes continued for about a day, sometimes for a couple of weeks. The vomiting became less and less, with increasingly long periods between the attacks



Fig. 1. Esophagus from a child of eight months old.

Fig. 2. Same case as in fig. 1, at 2 years of age.

of hematemesis. The last attack of vomiting and hematemesis occurred six months ago. His weight at birth was 2,700 g., at 1 year 5,700 g., at 2 years 9,250 g., and now, at a little over 3 years, 14 kg. He is lively and shows normal psychic development. Neither before nor after the attacks of hematemesis, nor during the intervening periods, have the liver and spleen been enlarged, a fact that was also confirmed by roentgen examination. No ascites was detected. Tuberculin tests and the Wassermann reaction were negative. Neither leukopenia nor thrombopenia have been present. Apart from slight anemia on his admission, the blood pattern in general has shown no abnormality. Roentgen examination of the esophagus revealed that the normal contour of the esophagus, with its longitudinal folds, was substituted by winding, tortuous vessels with large, irregular, rarefied sections and a remarkably wide lumen. (See figs.) Fluoroscopy revealed retarded evacuation.

In this case, nothing was found to account for the patient's

varices. Kleinschmidt, and others, have stressed the significance of navel infections or septic infections in some other part as a possible cause of changes in the portal vein. In one case described by Wallgren, in his work on splenomegaly in children, it is assumed that a navel granuloma, with the infection always associated with this disorder, might be the cause of vascular changes in the portal vein. The navel scar in our case was normal; nor were any other signs of infections observed. Changes in spleen, liver, or blood vessels have also been observed in connection with other infections such as erysipelas, whooping cough, angina tonsillaris, diphtheria, intestinal infection, and others, but no such infection is known of here. The Widal test gave a negative result. If there were stenosis in the portal region then spleen stasis might be expected, but the presence of splenomegaly is not obligatory, especially if the stenosis has developed gradually and thus created the conditions for the formation of anastomoses. We have not made an esophagoscopic examination. Roentgen examination of other parts of the alimentary canal have not revealed anything suggestive of angioma. Nothing to indicate liver damage has been obtained. With a high degree of probability the patient's esophageal varices are congenital.

As will be seen from this survey of the 14 cases in the literature, only the cases described by Vorpahl, Hansson, and myself, and possibly also the case mentioned by Schatzki and Holmes, may, critically speaking, be designated as congenital. In Vorpahl's case, the congenital deformity seems to be more in the nature of an angioma. In the few cases of angiomatosis intestinalis with its seat in the esophagus the condition sometimes appears as esophageal varices, on direct inspection and roentgen examination, and may give rise to bleeding. Benecke describes a case of this kind, stating that he also found angiomas in other parts. As mentioned earlier, purely local changes in the veins of the esophagus are a necessary condition for the development of congenital varices. These changes may be present in the form of a purely structural defect, a malformation, or they may have

arisen as the result of phlebitis, of nutritional disturbance in the vessel wall or some other similar factor. Some investigators, Thiefelder and Neelsen, for instance, stress the significance of nervous factors. They mention, among other cases, a case of tumor metastasis in the ganglion coeliacum, and in another case a hemorrhage due to trauma in the upper part of the splanchnic nerve. In both patients the veins in the parts adjoining these nerve areas showed phlebectasis, and this was considered to be due to deteriorated powers of resistance brought about by the damaged nervous regulation. Jaffé maintains that a weakness of the vessel wall is not sufficient to cause venous dilatation, but that the varices develop only after some additional provoking factor has arisen, usually in the form of a hindrance to the return flow of blood. Through this hypothesis, he endeavours to explain why phlebectatic conditions, although originating from congenital anomalies, make their first appearance later in life. To call such conditions congenital varices seems incorrect, however. In genuine congenital varices one does not expect to find stasis in the portal region (apart from the stasis due to the poor circulation in the varices). When the varices bleed, one does not expect a copious hematemesis such as occurs in the case of high pressure in the portal system together with a large spleen, when a hemorrhage resembles the evacuation of an entire dam when a sluice-gate is opened. In the case of these varices, the hemorrhage should be less severe, although the negative pressure in the esophagus may cause the bleeding to continue for some hours or days, though without the appearance of the copious, dangerous, evacuating hemorrhages occurring in connection with other esophageal varices. Another feature to expect with these varices is that the bleeding will occur less frequently, since a higher pressure in the vein must be regarded as a contributory cause of bleeding. Wallgren asserts that splenomegaly is not obligatory in stenosis of the portal vein or the vena lienalis, although it is one of the most characteristic signs in this disease. The absence of lienal swelling in stenosis of the portal vein would then be due to the presence of numerous anastomoses between the other vascular territories,

this prolificacy being the means of preventing stagnation in the vena lienalis. The condition for this development is that the stenosis should form very gradually, so that the capsular veins have time to re-form in sufficient numbers into substitute veins, and as long as the circulation functions well through these new channels there is no need to expect splenomegaly. But in the case of congenital varices, where the changes are already present at birth, a considerable pressure on the esophageal veins would need to be present to form these varices so rapidly, if a stenosis in the portal vein or the vena lienalis were the underlying cause. If such had been the case the spleen ought to have been enlarged, especially as, at this age, it ought to be able to increase in size with ease. In congenital varices, furthermore, the blood disorders in the form of leukopenia and thrombopenia, such as occur in stenosis in the portal vein due to various causes, cannot be expected to occur, since these are thought to be due to deterioration in the lienal function resulting from the stagnation. A secondary anemia, on the other hand, may of course arise. One reason why so few cases of congenital varices are mentioned in the literature may possibly be the insignificant bleeding as compared to that occurring in acquired varices originating from stasis, when the first manifestation of the disease is often dangerous and copious bleeding.

Summing up, it may be said that in congenital varices of the esophagus the following features are to be expected:

1. Small, early attacks of hematemesis, not copious, evacuating ones.
2. The varices are already present in the first month of life and are demonstrable by roentgenography.
3. A certain tendency to vomiting (as in Hansson's and my cases — probably owing to the cardio-esophageal relaxation and retarded evacuation often occurring in various types of esophageal varices).
4. No stasis in the portal vein or vena lienalis.
5. No blood disorders, with the exception of secondary anemia.

Although some patients with varices of the esophagus live for a long time, the prognosis seems to be bad. Each hemorrhage

is dangerous and may prove fatal. Splenectomy is performed in some cases in order to relieve the portal system, and the varices sometimes subside after this intervention. In acute hemorrhage constituting a threat to life, local tamponade treatment has been tried, and attempts have also been made to stop the bleeding by cauterization. Crafoord and Frenckner, in 1939, described their treatment of a 16 year old girl with severe varicose bleeding. Splenectomy had already been performed earlier, and on admission to the hospital the patient was in poor condition. Under esophagoscopic control, quinine-urethane was injected on three different occasions, with the result that the vessels gradually collapsed, and roentgen examination some time afterwards revealed an esophagus of normal appearance apart from the remains of a small varix at the base. The intervention had been performed three years before the case was published, and at the time of publication the patient was still without symptoms. In the United States, Moersch, in particular, has carried out many such treatments with successful results. In recent years, attempts have been made to produce shunt conduction between the vena lienalis and the vena renalis sin., with a view to lessening the load. We have not considered that there was any indication for these interventions in our case, where the signs and symptoms were so moderate and the risk of severe bleeding was slight.

Summary.

In connection with the description of a case of congenital varices of the esophagus in a child, the author has reviewed the literature on the subject and reached the conclusion that two or three of the previously reported cases were congenital while the others must be ruled out from this point of view. A number of criteria are set up for recognizing congenital varices of the esophagus.

Résumé.

En rapport avec description d'un cas de varices congénitales de l'esophage chez un enfant, l'auteur a relu la littérature relative

à ce sujet et il est arrivé à la conclusion que deux ou trois cas rapportés antérieurement était congénitaux, tandis que les autres doivent être exclus de ce point de vue. Un nombre d'indices sont énumérés pour identifier les varices congénitales de l'œsophage.

Zusammenfassung.

In Anschluss an die Beschreibung eines Falles von kongenitalen Oesophagusvarizen bei einem Kinde prüfte der Autor die Literatur über diesen Gegenstand und kam zu dem Schluss, dass 2 oder 3 der bisher berichteten Fälle kongenital waren, während die anderen von diesem Gesichtspunkte ausgeschlossen werden müssen. Es wird eine Anzahl Erkennungsmerkmale kongenitaler Oesophagusvarizen festgesetzt.

Resumen.

Al mismo tiempo que se describe un caso de varice congénita del esófago de un niño, el autor estudia la literatura médica existente sobre esta materia y llega a la conclusión de que dos o tres de los casos anteriormente descritos fueron congénitales, mientras que los restantes no pueden ser aceptados como tales. Se analizan varias opiniones para el reconocimiento de la varice congénital del esófago.

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CASE REPORTS

Toxoplasmosis in Children.

With reference to one particular case.

By

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Toxoplasmosis is an infectious disease, which, during the last ten years or so, has been discovered in man in an increasing number of cases, particularly in children during the first few years of life.

The disease, its causes, symptomatology, pathological nature and serology have been fairly well investigated, but not enough is known about its epidemiology and particularly therapy.

The following is an account of a case of toxoplasmosis in which we have evidence of neutralizing antibodies in the blood, not only of the mother, but of two other relatives.

CASE REPORT: A girl, now $2\frac{1}{2}$ years of age, born 1.6. 1945. The father is 27 years old and apparently in good health. He has been employed in the meat trade since 1943 and has lived in the same place since this date. He has always been healthy, completed his military service, has never had pneumonia, any protracted rise in temperature or gastric infection, nor to his knowledge received any tick bite. Neither in his parents' home, nor in his present one have there ever been cats, dogs or other household pets. — The mother is 24 years old. In her parents' home there were large number of rats and cats, and one year two cats died in a wasting disease. The mother has had most of the infectious childhood diseases, had pneumonia about the age of 10—11, but otherwise been well. She too, has no knowledge of any tick bite. Her pregnancy was normal but vomiting in the early stages was rather severe. The mother is again pregnant and expecting to be confined at the end of March or beginning of April 1948. As in the case of her earlier pregnancy there is again undue vomiting. Apart from the patient there are no other children in the family.

The girl was born about a fortnight before expected delivery in the maternity wing of a general hospital. The birth was normal. Weight at birth 2 670 grammes, length 49 cm. Head circumference 30 cm. Condition after delivery was normal. The hospital record states that the placenta

was normal. — Her mother states that the patient has had a squint from birth and has heard badly from infancy. The child began to reach for objects about the age of 6—7 months, sat up without support at 9—10, and could walk at the age of 16—17 months. She can speak isolated words but no sentences.

At the first attack of convulsions the patient was admitted to the medical wing of the above mentioned hospital in March 1946. She was then 9 months old. On admission to the hospital there was rotary nystagmus, squinting and slight jerking of the fingers. A lumbar puncture showed conditions to be normal. She was mentally deficient. The girl was discharged after two days at the request of her parents. Later at home she had convulsions in the arms and legs with a short interval of unconsciousness. In the same year in the middle of August the patient was readmitted to the medical wing of the same hospital, with fresh convulsions. Roentgenograms of the skull showed marked intracerebral calcifications, as before there was marked mental debility, but otherwise nothing specifically neurological. She was discharged after a few days and the parents informed that there was the greatest likelihood of grave cerebral injuries.

In November 1946 the parents saw an oculist (dr. G. Klang) on account of the girls' squint. On making his examination he found large round atrophical patches with pigmentation in the choroid, one in the fundus of the left eye near the macula. No active chorioretinitis. The changes in the patient were at this time, that is, when she was 1 year and 5 months old, of long standing.

Since her discharge from the hospital in August 1946 the patient has had 3 fits with unconsciousness and convulsions of the same nature as before. Her case was referred for investigation to the Department of Pediatrics in Lund.

Condition: At the time of her admission on the 16.9. 1947 the patients' general condition was good, physically fairly satisfactory. Weight 13.2 kg. Nothing pathological about the internal organs. Neurologically she was found to have a leftsided, convergent squint, rotary nystagmus and decreased hearing. Reflexes normal. Tension unincreased, gait somewhat insteady, but otherwise normal. The fontanelle closed. Head circumference 47 cm. Mental development plainly retarded. Special examination of the eyes (dr. M. Peil): No microphthalmus. Double, multiple, extensive chorioretinitis with a large central area at the fundus of the left eye near the macula. The latter is considered to be the cause of her squint. The pupil reflexes were normal. A renewed examination about a month later revealed the condition to be unchanged. The change being of long standing. Otologically (dr. L. Gisselsson) loss of hearing was established, but how great and of what nature was impossible to determine owing to the indifferent cooperation of the patient.



Figure 1.

Roentgenograms of the skull showed marked areas of intracerebral calcifications situated in the choroid plexus or basilar ganglia. When compared with the photographs from the roentgen examination of the previous year there was no evidence of the calcifications having increased. Encephalography showed a marked hydrocephalus internus with considerably enlarged lateral ventricles. (docent O. Olsson) (Figure 1). — Repeated tests showed the lumbar fluid to be clear it did not contain any cells, and there were negative albumen reactions. W. R. in cerebrospinal fluid was negative. Blood count, examination of the urine and sedimentation rate, all revealed a normal condition. Mantoux 1 mg negative. X-ray examination of lungs, normal.

Serological examination — clinical diagnosis of toxoplasmosis — was carried out by professor S. Gard of the State Bacteriological Laboratory at Stockholm, and yielded the following result, that there was evidence of neutralizing antibodies against toxoplasma in the patients' serum. The tests were carried out on the girl on two separate occasions. In the mothers' blood too, there was a strong concentration of neutralizing antibodies against toxoplasma. No inoculation experiments have been carried out on animals.

To sum up then, this patient presents the following anamnesis and condition: A squint from birth and early deterioration in hearing, convulsions and retarded mental development. On the clinical side we have hydrocephalus internus, intracerebral calcifications, chorioretinitis, deteriorated hearing, suggested microcephalus and mental debility in addition to toxoplasma neutralizing antibodies in the blood. The symptoms shown clearly correspond with those of toxoplasmosis.

The symptomatology in toxoplasmosis is mainly as follows. In children the disease occurs as congenital encephalomyelitis, which either appears in the first few days post partum and which then in most cases leads quickly to death, generally in the first few weeks of life, or a fatal outcome is not immediate, but the disease does not reveal itself until later and with characteristic symptoms. Hydrocephalus internus, cerebral calcifications, retinochorioiditis, microcephaly, and microphthalmus also convulsions and mental debility. This is the most usual form, even if the above mentioned symptoms are not all present at the same time. In both forms positive pathological discoveries are made in the lumbar fluid. Yet there are cases, such as the writers' own, in which normal conditions are present.

A few cases of toxoplasmosis have been established in children of school age. These have run their course with atypical encephalitis with fever, convulsions and pleocytosis in the lumbar fluid.

In adults the disease appears in isolated cases as an acute fever with a rather typical exanthem of the so called Rocky-Mountain-spotted-fever type as well as atypical pneumonia, then there is also a latent subclinical form in, amongst others, mothers and eventually other relatives of children with toxoplasmosis, where the disease can be proved serologically only by the presence of neutralizing antibodies. It is considered that the transmission of the disease by these clinical healthy mothers to the children occurs in utero in the later stages of pregnancy, about the 3rd—7th month. However the further pathological-anatomical occurrence had not yet been determined. Attempts have been made to infect pregnant monkeys, but as yet without success. (WOLF and COWEN (1), 1945).

The above mentioned symptoms and symptom complexes have been more or less pronounced among the 45 or so cases hitherto mentioned in medical literature. The honour of having analysed those experiences which have so far been gained concerning toxoplasmosis in children must primarily go to such names as the scientists, WOLF, COWEN, and PAIGE (1, 4, 5, 6, 7) also SABIN (2, 3, 8, 9, 10, 11) and his colleagues. The three first mentioned writers have analysed the symptomatology and pathological anatomy of the congenital form of toxoplasmosis in a series of writings in the years 1937—1945 and are also the first to have succeeded in transmitting toxoplasma from a human being to an animal (1939). In addition to the cases published by themselves, Wolf, Cowen and Paige have been

able to prove toxoplasmosis in 4 earlier cases published by other writers (12, 13, 14, 15) in which toxoplasmosis symptoms were present, but where these writers had failed to make this diagnosis. Congenital toxoplasmosis has later been described by several other writers during the last few years, among them SABIN (8), LEVIN and MOORE (16) (1942), CROTHERS (17) (1943), STEINER and KAUMF (18) (1944), ZUELZER (19) (1944), DEW (20) (1945), PRATT-THOMAS and CANNON (21) (1946) from America. In Europe BAMATTER (22) (1946), ROBINSON (23) (1947), GLANZMAN (24) (1947) and FREUDENBERG (25) (1947) amongst others, have published cases in Switzerland (Robinsons' case actually from Italy) and MAGNUSSON (26) one from Sweden 1947. In addition there is yet another case from Sweden (personally mentioned by dr. SMITT (27)). DRENOWSKI (28) has found toxoplasma in the blood of a patient in Bulgaria, but does not mention clinical symptoms.

In 1941 SABIN (8) gave an account of the two definitely certain cases of toxoplasmosis in older children.

PINKERTON (29, 30) together with WEINMAN (29) (1 case, 1940) and HENDERSON (30) (2 cases, 1941) has published the first cases of toxoplasmosis diagnosed in adults, Later SYVERTON and SLAVIN (31) 1946 have given an account of one case.

MILLER (32) in 1947 described a case of congenital toxoplasmosis, and in this connection gave an account of 38 known cases of toxoplasmosis, including all age groups. In this survey the European cases of the disease amongst others, have not been included. With the case published in the present work the number of cases described would amount to 49.

As toxoplasmosis has shown a considerably high mortality rate in those cases hitherto described (of 17 cases stated in 1942 only 4 survived. SYVERTON and SLAVIN (31) report 1946, that only 2 cases survived out of 36) attempts have been made to find suitable means of treating the disease. SABIN (10, 11) and his colleagues have examined the toxoplasmaic properties of several different chemotherapeutics. The result of these investigations reveal that the sulfa-type chemotherapeutics provide the means of arresting the disease in animal experiments. Sulfapyridine and sulfathiazole have been tried in some human cases, SABIN (8) also DEW (20) and others, but only with temporary effect. Primarily, at least in the congenital cases in which calcification, chorioretinitis, etc. are present already at birth, hardly any success is anticipated from this type of sulfatherapy. In these cases the mother should be treated early in pregnancy. No such cases have been published to the writers knowledge.

Discussion: The case of toxoplasmosis described above may be attributed to the congenital form of the disease. Amongst other things, the fact that the patient squinted from birth points to this. Of course

squinting during the first 3—4 months is quite common in infants, but considering that this squint has persisted all the time, it must be considered probable that the cause of the strabismus has been the same throughout, that is the changes in the eye fundus of the patient. The chorioretinitis with the central area in the left eye completely explains the patients' leftsided squint. As other toxoplasmosis cases have revealed that the chorioretinitis is present already at birth, the same is considered to be very likely in this patients' case. When the girl had her eyes examined for the first time, at the age of 1 year and 5 months, the chorioretinitis was of long standing, which fact also supports the above conclusion. In addition there were intracranial calcifications at the age of 14 months — which roentgenograms revealed to be unchanged 1 year later —, mental debility was also apparent already at 9—10 months. If the disease had been developing when the patient first had convulsions (age 9 months) positive reactions would have been found in the lumbar fluid. The fact that the mother too has neutralizing antibodies in her blood also points to the obviously congenital nature of the disease.

The nystagmus which was diagnosed in the patient may also be explained by the changes present in the eye fundus, and is therefore of an optical nature.

The girls' reduced hearing must be considered to arise from the same cause as the other symptoms. Cases of this nature with injuries to the VIIIth nerve have been described (ADAMS, HORNS and EKLUND (33)) even if loss of hearing is not otherwise one of the usual signs of toxoplasmosis. With knowledge of how the virus is spread and its affinity to nearly all living tissue, it should not be too difficult to imagine a causative connection with regard to this symptom.

In order to form an opinion as to how the mother was infected and to ascertain a possible spreading of the infection in the family, whereby some knowledge might be gained of the epidemiology of the toxoplasmosis disease, the writer has examined the following of the patients' relatives, her parents, her grandparents on her mothers' side, those on her fathers' and two aunts. In this connection an amnesia has first of all been made with special attention to the appearance of any form of gastro-intestinal symptoms, protracted fever condition, pneumonia or any peculiar exanthem, such symptoms as have been present in the few mentioned cases of adult toxoplasmosis. In addition the presence of domestic animals has been noted, particularly dogs, cats, mice and canary birds, all of which may be infected with toxoplasmosis and thus act as hosts for the virus. The writer has also enquired whether any members of the family might possibly have been bitten by ticks, as it has been particularly stressed in some quarters, that toxoplasmosis may possibly be transmitted through tick bites. The patients' relatives have also been subjected to a general examination, including ophthalmoscopy and blood count (hemoglobin after Authenrieth, a count of the white corpuscles and differential count).

Finally, and as the most important factor in the investigation, a serological examination was made (prof. Gard, Stockholm) to determine the presence of neutralizing antibodies in the blood.

The result of the lastmentioned examination are mentioned first, as being the most valuable and are illustrated in the diagram below (figure 2).

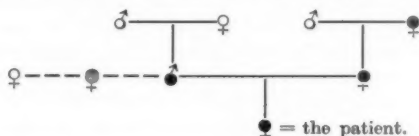


Figure 2. The shaded figures denote positive, those containing vertical lines uncertain neutralization test.

With regard to the remaining questions asked, the following result were obtained. In the home of the mothers' parents, there were as has been mentioned before, both cats and rats, and in 1942 or 1943 — a more definite date could not be obtained — a couple of cats died from a wasting disease. The patients' father visited this house on several occasions at this time. However none of the members of the family could recollect having been bitten by ticks either at this time or on any other occasion, neither were any of them ill at this time. The patients' grandfather on her mothers' side, who showed a negative neutralization test had had one attack of convulsions at the age of 4 — no further attacks — and her mother had pneumonia at the age of 10, otherwise all those examined had been in good health and able to work, except for common infections and other illnesses, which cannot be considered of any importance from toxoplasmosis angle. These investigations then did not yield any definite evidence that those persons with positive serological reaction had been ill when they contracted the toxoplasmosis disease.

Ophthalmoscopy revealed normal condition in all. Blood tests yielded normal results in all those with a positive reaction except in the mother who showed slight anaemia (hemoglobin 73 %) and who also showed a sedimentation rate of 20 mm/1 hour (note her pregnancy). The fathers' sedimentation rate was normal.

As illustrated in figure 2, it was the patients' parents and her maternal grandmother who had toxoplasma neutralizing antibodies in their blood. One aunt, who had otherwise always been well, revealed an uncertain reaction. The question which immediately arises, is, when were these persons infected? We have the following possibilities. The patients' maternal grandmother may have passed the disease on to the mother, which ran its course unnoticed in the latter, and symptoms have arisen first in the third generation. This possibility however does not explain why the father has the disease, and is not very likely for a number of other reasons.

Another possible explanation could be that the maternal grandmother and the mother contracted the disease on one occasion, while the father was infected on yet another. This involves a rather considerable spreading of the disease. Finally, the following may possibly be the explanation. The girls' maternal grandmother, as well as her parents were infected with toxoplasma on one and the same occasion. This could have been in the home of her maternal grandparents at the time, when the above mentioned domestic animals died. This viewpoint presupposes the animals to have been toxoplasma infected. Furthermore her maternal grandfather would in this case also have been infected. There may of course be other possible sources of infection (i. e. the father may have been infected in the course of his work), but the three mentioned above seem to the writer to be those most worthy of mention.

In conclusion then it is clear that this investigation does not yield any certain evidence of how these three members of the family became toxoplasma infected. It appears most likely that all three were infected on the same occasion. If this was at the above mentioned time, when the cats died, cannot be stated with certainty, and must remain only a hypothetical conjecture. Consequently this investigation has not yielded any conclusions of more definite value to the epidemiology of the toxoplasmosis disease. It can only be proved that the disease — as also in several earlier cases — appears among relatives of toxoplasmosis cases without showing clinical symptoms. The investigation verifies that the disease is more widespread than was at first reason to believe.

In the present case the mother, as has been mentioned earlier, is once again pregnant. These circumstances have given rise to some speculation. Obviously there is a risk that this child too may be infected in utero, and thus be born with manifest congenital toxoplasmosis, or the disease may possibly break out later. However it has been stated that after a toxoplasmosis case healthy children may be born, who may continue to remain clinically healthy in the future, even if a serological examination should yield positive neutralization tests (ADAMS, HORNS and EKLUND (33)). With siblings of this kind however one never knows if the disease will break out later. Previous experiences are still too inadequate. As it has been found possible to control the disease in experimental animals by means of sulfapreparations, and it has been suggested from the clinical side, that sulfapreparations should be tried in suitable cases, it was considered in the clinic appropriate, for safety's sake, to treat the mother during the pregnancy with sulfathiazole, in order to possibly counteract a toxoplasma infection in the foetus, should any such infection be present. A detailed examination of the coming child will of course be made post partum.

Summary.

The writer gives an account of a typical case of congenital toxoplasmosis of a girl $2\frac{1}{2}$ years old.

An investigation revealed that both the mother and the father as well as the maternal grandmother, all of whom were clinically healthy, revealed positive neutralization tests against toxoplasma. The remaining examined members of the family were negative, except for an aunt who showed uncertain reaction.

The mother is again pregnant. Sulfathiazole treatment of the mother has been started.

Résumé.

L'auteur donne un rapport sur un cas typique de toxoplasmose congénitale chez une jeune fille de 2 ans et demi.

L'examen a révélé que la mère et le père ainsi que la grand'mère maternelle qui étaient tous en bonne santé cliniquement montraient des tests positifs de neutralisation contre le toxoplasme. Les autres membres de la famille qui furent examinés étaient négatifs, excepté une tante qui montrait une réaction incertaine.

La mère est de nouveau enceinte. On a commencé à la traiter au sulfathiazole.

Zusammenfassung.

Ein typischer Fall kongenitaler Toxoplasmose bei einem $2\frac{1}{2}$ -jährigen Mädchen. Eine Untersuchung ergab, dass sowohl die Mutter und der Vater, als auch die mütterliche Grossmutter, obwohl alle klinisch vollkommen gesund waren, positive Neutralisationsproben gegen Toxoplasma zeigten. Die übrigen untersuchten Familienmitglieder waren negativ, mit Ausnahme einer Tante, welche eine unsichere Reaktion ergab.

Die Mutter ist wieder schwanger. Sulfathiazol-Behandlung wurde begonnen.

Resumen.

Se informa sobre un caso típico de toxoplasmosis congénita en una niña de dos años y medio. Se comprobó que tanto la madre como el padre y la abuela materna, todos clínicamente sanos, manifestaban reacciones positivas contra toxoplasma. Los otros miembros de la familia que fueron examinados resultaron negativos, con excepción de una tía que tenía reacción dudosa. La madre está preñada de nuevo. Ha empezado un tratamiento de sulfatiazol.

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Penicillin Treatment in Congenital Syphilis.

Report of five cases.

By

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During the last few years penicillin has been widely used in the treatment of congenital syphilis. The most satisfactory results have occurred in the younger age-groups, while the effect of the drug on the late manifestations of the disease does not seem to be so gratifying. In the great majority of cases of early congenital syphilis a satisfactory outcome has been obtained following a single course of penicillin. As a rule, the clinical signs of infection clear with great rapidity during or soon after the treatment, while the change to seronegativity is often delayed for several months. The presence of cerebrospinal abnormalities does not seem to give a bad outlook. Clinical or serological relapses have hitherto been rather infrequent. Herxheimer reactions are relatively rare and there does not seem to be any justification for gradually increasing dosage at the beginning of treatment. The proper dosage is not yet established. Most authors recommend a total amount of at least 100 000 units per kg body weight given over a period of twelve to fifteen days.

In this country congenital syphilis is a rare disease and our experience with penicillin therapy, therefore, rather limited. A report will here be given of five cases of congenital syphilis treated during the last two years at Kronprinsessan Lovisa's Children's Hospital.

Case 1. No. 457/46. B. L., a girl born in March 1946 with a birth weight of 2580 g, was first seen when she was 1 month old. At this time it was not known, that both parents had treatment for syphilis and the girl did not show any signs of disease. At the age of three months she was admitted to the hospital on account of abdominal distension, fatigue and loss of appetite. She was found to have ascites, anemia, slight periostitis of the long bones and a positive Wasserman test. As soon as diagnosis was established penicillin was given over a period of 24 days with a total dosage of 180 000 units per kg body weight. The result was very satisfactory. Ascites and anemia improved and the serologic titer markedly declined during the treatment. The girl was sent home and was not seen until 4 months later. Now there were no clinical symptoms of syphilis and the Wasserman reaction had become negative. The spinal fluid, which had not been examined before, likewise showed a nega-

tive serologic test. Still, one and a half years after penicillin was given no clinical or serological signs of relapse have occurred.

Case 2. No. 349/46. L. L., twin-sister of the forementioned patient. On account of prematurity (birth weight 1500 g) she was in ward at the hospital during her first 7 weeks of life. At this time she seemed to be in good health except for a slight anemia, which was thought to be related to the prematurity. When the sister was admitted (see above) the patient, too, was examined as being an identical twin and, like her, was found to have ascites, anemia, periostitis and a positive Wasserman reaction. A single course of penicillin was given over a period of 23 days with a total dosage of 145 000 units per kg. The clinical symptoms improved but she was still strongly seropositive after completion of treatment. The girl was sent home and was not re-examined until 4 months later. She now seemed to be quite well and had become seronegative. No abnormalities were seen in the spinal fluid (examination had not been made previously). Still, one and a half year after treatment, there are no signs of relapse, neither clinically nor serologically.

Case 3. No. 863/43. K. H., a boy, was born at full term in July 1943. It was not recognized that the mother was infected until soon before delivery. At the age of 2 months the boy was found to have pseudoparalyses of both arms. There were marked osteochondritic changes and a moderate degree of anemia. The blood Wasserman and flocculation tests, which were negative at birth, had become strongly positive. The spinal fluid was not examined. After treatment with arsenic and bismuth the clinical symptoms subsided but the serologic tests were still positive. On the second admission, at the age of 6 months, the boy seemed to be in perfectly good health and the Wasserman titer had decreased; the flocculation tests, however, were as strongly positive as before. Examination of the spinal fluid did not reveal any abnormalities except for a positive reaction of Meinicke. This became negative following a second and third course of arsenic and bismuth and remained so on all subsequent examinations. As regards the blood, however, no further regress of the serologic reactions was seen. Mercury and acetarsol had but a transient effect. When the boy was readmitted in August 1946, at the age of 3 years, the Wasserman as well as the flocculation tests were still positive. Now, penicillin was given over a period of 12 days with a total dosage of 120 000 units per kg body weight. Six weeks after completion of treatment the Wasserman reaction became negative; the flocculation tests, however, remained positive. In December 1946 a second course of penicillin was given with a total amount of 100 000 units per kg. 1 month later the flocculation tests became negative for the first time, and on the last examination, in Dec. 1947, there were still no signs of serological relapse.

Case 4. No. 1192/46. L. O., a boy, was born in Oct. 1946, 4 weeks

before full term, the birth weight being 2350 g. At the age of 4 months he was admitted on account of icterus. Examination showed hepato- and splenomegaly, ascites, anemia, osteochondritis and abnormalities of the spinal fluid. The Wasserman reaction was strongly positive. Penicillin therapy was started as soon as diagnosis was established. The patient was, however, in a very bad condition and died on the ninth day after beginning of the treatment. The diagnosis of syphilis was confirmed at autopsy. Death does not seem to have been related to treatment. The total dosage given was 55 000 units per kg body weight.

Case 5. No. 804/40. S. Z., a girl born in Dec. 1931. Her mother had been treated for syphilis several years previously. During pregnancy no serologic examination was made and no specific treatment was given. The child was born at full term and seemed to be in good health. From the age of 4 years she was under medical care on account of educational difficulties. In Sept. 1940 she was found to have Argyll-Robertson pupils and a positive reaction of Wasserman. On admission she was in a good general state and except for the pupil changes, atrophy of the left optic nerve and slight abnormalities of the spinal fluid, there were no stigmas or symptoms of syphilis. The Wasserman and flocculation tests of the blood as well as of the cerebrospinal fluid were strongly positive. During the following years she was intensively treated with fever therapy, arsenic and bismuth and in 1943 the Wasserman test became negative. However, the flocculation tests remained positive. She was in good health all the time and no symptoms of juvenile paresis were seen. In June 1947 the girl was re-admitted for penicillin treatment. The drug was administered over a period of 10 days with a total dosage of 75 000 units per kg body weight. In addition bismuth was given. No immediate effect was seen, the flocculation tests being still positive 4 months after completion of treatment.

Summary.

A report is given of five cases of congenital syphilis treated with penicillin. Satisfactory results were seen in three cases (no. 1—3). Death occurred in one case (no. 4) during treatment. In one case (no. 5), finally, enough time has not elapsed for proper conclusion.

Résumé.

Rapport de cinq cas de syphilis congénitale traités par la pénicilline. On a constaté des résultats satisfaisants dans trois cas (no. 1—3). Un cas de mort (no. 4) pendant le traitement. Dans un cas (no. 5) il ne s'est pas écoulé assez de temps pour faire une conclusion juste.

Zusammenfassung.

Bericht über 5 mit Penicillin behandelte Fälle von congenitaler Syphilis. In 3 Fällen (Nr. 1—3) war das Resultat zufriedenstellend. Ein Patient (Nr. 4) starb während der Behandlungszeit. In einem Fall (Nr. 5) war die Zeit zu kurz, um einen sicheren Schluss ziehen zu können.

Resumen.

Se informa sobre 5 casos de sífilis congénita tratados con penicilina. En 3 de los casos (1—3) el resultado fué satisfactorio. En el caso número 4 el enfermo falleció durante el tratamiento. En el caso núm. 5 no ha transcurrido todavía suficiente tiempo para poder formular conclusiones.

Literature.

PLATOV, et al., J. A. M. A. 133: 10, 1947. — ROSE et al., Wyvell, Dorothy (Abstracts in the 1947 Year Book of Pediatrics.)

A case of Sprue in the later childhood treated with folic acid.

By

L. STRÖM, Lic. med.

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Head: Prof. A. WALLGREN.*

In September 1946 a boy, born in 1932, was admitted to the Pediatric Clinic of the Norrtull Hospital in Stockholm. His history of illness was as follows.

Hereditary nothing of interest. Weight at birth 4 000 g. Breast feeding for three months, after that milk mixtures. Pneumonia at five. Morbilli and epidemic parotitis during the first years at school. Otherwise on the whole healthy till November 1945. He then began to be more and more tired, having a bad appetite. No local symptoms. Could continue his schoolwork. In March 1946 influenza with fever, diarrhoea and vomiting — stayed in bed a week — after that the evacuations became loose and lighter in colour, sometimes watery, usually sticky. Bowels 2—3 times sometimes only once a day. No tenesmes. Vomited after almost every meal. Became thinner — has never been fat — got hollow cheeks. Several doctors were consulted and finally, on the ninth



Fig. 1. G. A. on the 11th of September 1946.

of April, he was admitted to a hospital. Discharged after a week with the direction, that he could start going school again. The diagnosis was: Observatio, Anemia sec. Hemoglobin was 74 per cent. Red blood cells 3.8 millions. Gastric analysis showed achlorhydria. Stools showed nothing abnormal. No fever. At the end of the spring his state of health was the same with regards to the evacuations. His appetite bad and he could not play with his friends. Recovered a little in the summer, had only one evacuation a day, a little looser than normal. No diet, but tried to avoid fat food. Ever since March he had often had painful aphtous vesicles in his mouth and on the tongue. Had been taking iron compounds all the winter.

On the ninth of September he was admitted to the Clinic.

Condition at arrival: Slow in movements, had a tired look. Cachexia. Dry, peeling, brown-pigmented skin, especially at the areolae mammae, on the cheeks and on the abdomen. Hollow cheeks. Pronounced muscle atrophy. No edema. Clubbing of the fingers. Along the whole edge of the tongue and in buccae small white vesicles with reddened margins. Tonsils 0. Heart: physically 0. Blood pressure 85/60. Lungs 0. Abdomen: Liver and spleen not palpable. Nervous system: tendon and periosteal reflexes weak. No paresis. (Fig. 1.)

Laboratory data.

Blood examination revealed the following: red blood cells 1.9 millions, hemoglobin 58 % (Zeiss), Index 1.53. White blood cells 2 700. Differential count: band neutrophils 7 %, segmented neutrophils 34 %, eosinophils 1 %, lymphocytes 56 %, monocytes 2 %. Aniso- and poikilocytosis.

Differential bone marrow count: metamyelocytes 18 %, myelocytes 10 %, band neutrophils 5 %, segmented neutrophils 33 %, eosinophils 5 %, lymphocytes 29 %. — Megaloblasts none, young erythryblasts 17, late erythroblasts 35, normoblasts 79 in 100 white cells.

Reticulocytes 5 %.

Platelets 71 000.

Protrombin index 57.

Time of bleeding 9 minutes. Time of coagulation: 5 minutes. Red-cell fragility in hypotonic salt solutions was not increased. Bilirubin (Meulengrachts method) 1 : 13.

After ingestion of glucose a characteristic flat blood sugar curve (fig. 2).

Serum proteins: total 4.5 per cent, albumin 2.8 %, globulin 1.7 %.

Serum iron 0.112 mg%, Kalium 22 mg%, Natrium 306 mg%, Calcium 9.7 mg%, Phosphatase 5.8 units.

Gastric analysis: a fasting specimen of the stomach contents gave a determination of free hydrochloric acid 0, total acidity 28.

Glucose tolerance test.

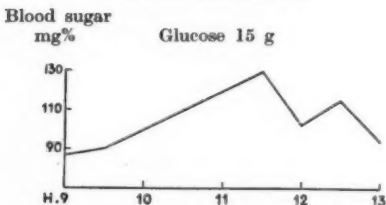


Fig. 2.

Stools: yellow, semiliquid, voluminous. Mucus 0. Blood 0. Threads of muscles. The fat formed 68 % of the solid matter.

Nonprotein nitrogen 50 mg%. Wassermann reaction negative.

X-ray examination:

Lungs, no comments.

Abdomen, probably diminished spleen.

Colon, no comments.

Long bones, no alteration.

Electrocardiogram. Rate 88. P—Q 0.14", QRS 0.05", Q—T 0.3", no preponderance. T-waves iso-electric. Myocardial injury.

Here was thus an illness with steatorrhea, an extreme thinness and a hyperchrom anemia as principal symptoms. Furthermore the patient showed a rich flora of various symptoms, forming a picture that corresponded very well with that of non-tropical sprue.

The course of illness: The patient who all the time was un-febrile—sub-febrile and had a normal sedimentation rate of red blood corpuscles was put on a carbohydrate-rich diet which to begin with chiefly consisted of bananas, and later on in addition was given Arobon (the flour of the beans of *Ceratonia siliqua* from Nestlé Products Co., Switzerland), 200 g per day, and furthermore 10 g aminosolglycose (Magnusson) per day. His general state of health was quickly improved and the weight was steadily increasing. There also was an increase in the number of red cells, while the hemoglobin was unchanged. The evacuations were also about the same, voluminous as a rule and loose. After a month a certain stagnation was attained, when a treatment with folic acid was started, which was kindly enough placed at our disposal by Dr. med. Jan Waldenström in Upsala. The dose was 5 mg 5 times a day for three days, after that 5 mg 3 times a day. Two days later the patient had normal stools which after that remained normal. The increasing of weight made new progress and the improvement proceeded day by day. His diet was increased without any influence on the stools. On the other hand no change of the blood-picture worth mentioning was observed besides an increase of the reticulocytes. (Fig. 3.)

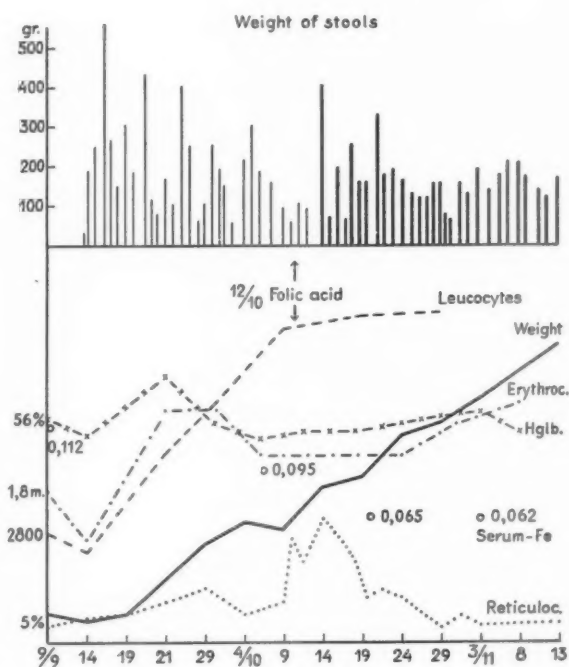


Fig. 3.

At the time of discharge the patient weighed 27 kg and showed an entirely different picture from the one at the arrival (Fig. 4). Four months after the discharge he has per letter told that he weighed 35 kg, was feeling well and could take part in his schoolwork without any difficulties. Avoids fat food but does not follow any certain diet.

Of interest in this case, apart from the treatment, is on one hand the short history of illness, on the other the patient's age, of which the latter might be considered to illustrate Hess Thaysen's nowadays generally accepted unitarian opinion that the three states of illness — tropical sprue, non-tropical sprue and coeliac disease — are identical, as well with regard to ethiology as to pathology and clinical signs and symptoms.

Thus, the coeliac disease would be the form in which the sickness appears in small children with their special characteristics e. g. the

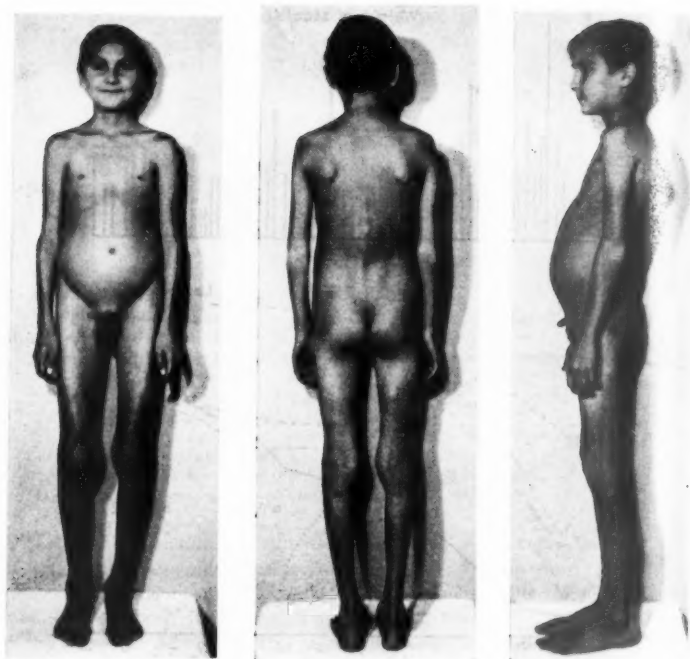


Fig. 4. G. A. on the 9th of November 1946.

serious disturbances in the balance of fluid depending on the child's special physiology.

A great many cases of sprue, respective coeliac disease, have been published during the last years. Of these I have, however, not found any case of sprue that has started so early with symptoms characteristic for this very sickness. Many cases of sprue at adult age are described which have started as coeliac disease in the very early childhood. Still Røe describes a case of sprue in a girl of 9 who had had symptoms for 4 years. In this case it would probably be just as correct to speak of coeliac disease.

Therapeutically the patient offers more of interest. Folic acid has as a rule been used in treatment of macrocytic anemias. Experiences of treatment of non-tropical sprue and coeliac disease with folic acid, however, have lately been published. Carruthers et al. describes 4 cases of

hypochromic anemia which he tried to treat with folic acid. The anemia, however, was not influenced, though the patients in a few days recovered from the chronic diarrhoea which was the principal illness in 2 of the cases. He then treated 6 cases of serious diarrhoea with folic acid and after 2—5 days' treatment he got moulded stools in every case. Garcia Lopez et al. are reporting 18 cases of sprue which they — principally because of the macrocytic anemia, occurring in these cases — had treated with folic acid. They got a prompt regeneration of the blood and a tendency of the alimentary tract to return to normal function. In our case there was no evident macrocytic anemia in spite of the high index in the beginning, which might explain that the effect of folic acid on the blood picture was so slight.

Summary.

A case of typical sprue in a boy fourteen years of age is described. Treated with folic acid, 5 mg 5 times a day for three days, after that 5 mg 3 times a day. Prompt increasing of weight but no change of the blood-picture besides an increase of the reticulocytes. Discharged in a very good general condition without any symptoms of his illness.

Résumé.

Un cas de sprue typique chez un garçon de 14 ans. Traité par «folic acid», 5 mg 5 fois par jour pendant 3 jours, puis 5 mg 3 fois par jour. Augmentation immédiate du poids, mais aucun changement dans le sang, sauf une augmentation du réticulocytes. Renvoyé de l'hôpital dans une condition générale très bonne sans aucun symptôme de cette maladie.

Zusammenfassung.

Ein typischer Fall von Sprue bei einem 14jährigen Knaben wurde mit Folic acid behandelt (5 mg 5 mal täglich durch 3 Tage, dann 5 mg 3mal täglich). Prompte Gewichtszunahme ohne Änderung des Blutbildes ausser einer Zunahme der Retikulozythen. Patient wurde in sehr gutem Allgemeinzustand ohne äussere Zeichen der Krankheit entlassen.

Resumen.

Un caso típico de psilosis en un muchacho de 14 años. El enfermo recibe un tratamiento de ácido «folic», 5 mg 5 veces al día durante tres días y después 5 mg 3 veces al día. Se observó un rápido aumento del peso, pero ninguna alteración del cuadro hemático, y además un aumento del reticulocito. Salió del hospital en muy buenas condiciones generales y sin ningún síntoma de la enfermedad.

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BOOK REVIEW

HELEN B. TAUSSIG, M. D., **Congenital Malformations of the Heart.**
The Commonwealth Fund. New York 1947.

Maude Abbott, from Canada, and Helen B. Taussig, from the United States, have furthered the modern evolution of congenital heart disease more than anyone else. Maude Abbott was a pathologist and it was she who introduced the classification of cardiac malformations with regard to the degree of cyanosis. Helen Taussig's work is based upon Abbott's but she has chosen a different approach to obtain her results. Dr. Taussig is a clinician and all of her work has the clinical aim to diagnose every special cardiac malformation in life with the help of her own methods. Indeed, fluoroscopy is her method of choice. Today most of the heart defects can be accurately diagnosed by Dr. Taussig in front of her fluoroscopic screen.

Dr. Taussig is the founder and the head of the Cardiac Clinic at Harriet Lane Home of The Johns Hopkins Hospital in Baltimore. The result of her many years of experience and hard work, as far as congenital heart disease is concerned, is collected in the monography published at the end of 1947.

The book has three parts. The first deals with physiological and methodological problems. Physical examination, fluoroscopy, x-ray examinations and electrocardiography are all carefully described. As mentioned in the preface there is but little discussion of other methods, such as, angiocardiography, catheterization of the heart, circulation time studies, phonocardiography, gas analysis, chest lead electrocardiograms

and arterial pulse curves, in spite of the fact that these diagnostic aids are in many cases of the greatest clinical value. Many of these methods demand team work and Dr. Taussig has done most of her outstanding work alone. That is both her great merit and her limitation. The first part of the book is concluded with a chapter on cyanosis, extraordinarily well planned and full of important information.

The second part is concerned with the cyanotic cases. In every malformation in this part, as well as in the acyanotic cases, the author takes the fetal and postfetal circulation and the stress it makes on different parts of the heart as a basis for further discussion. By doing so she is able, mostly by means of fluoroscopic diagrams, to give every malformation its clinical picture. There are perhaps too many circulatory and fluoroscopic diagrams in the book. The ref. would have preferred to have still more roentgenograms in the text. The most important chapters in part two are the defective development of the right ventricle with tricuspid atresia, the tetralogy of Fallot, the complete transposition of the great vessels, the truncus arteriosus and the single ventricle. The ref. is somewhat doubtful that there are real possibilities to make the special diagnosis in every single case. Let us take as an example the extreme dextroposition in the cases of pulmonary atresia. In the author's opinion these patients could live only as long as the ductus arteriosus is patent. The ref. has recently seen a 4 year old girl with pulmonary atresia, extreme dextroposition of the aorta and a ventricular septal defect but without a patent ductus arteriosus. The case was examined by autopsy. This case must represent a compromise between an extreme tetralogy of Fallot and the group mentioned above. The ref. has taken this example in order to point out that reality often shows transitions not compatible with a systematic classification in groups and subgroups. This fact does not lessen the value of the fluoroscopic work of the author, which, to a high degree, has increased our knowledge in this field.

The third part of the monography deals with the acyanotic cases. It is a little astonishing to find the Eisenmenger complex in this part of the book and not among the cyanotic cases. It is true that many Eisenmenger cases show no cyanosis, especially in early childhood, but as far as there is any overriding aorta, this group should have been placed in part two of the book.

The patent ductus arteriosus is presented in an extensive chapter. The author stresses that only cases with a typical continuous murmur should be operated upon. However, she states that many patent ductus cases in infancy and early childhood show systolic instead of a continuous murmur. Although this is true regarding some cases, in the opinion of the ref. it is by no means the rule. The author differentiates a thrill from a murmur not only in this chapter but consistently throughout the book. There is, however, no real difference between the two phenomena,

as a thrill is only an evidence that a murmur has such an intensity as to make the vibrations of the chest wall palpable. (ref.)

The defects of the auricular septum and ventricular septum are open to an extensive representation as is the coarctation of the aorta. In the latter malformation the Crafoord operation should be performed in cases of extreme hypertension and if the patient develops subacute bacterial endocarditis. The author writes: »Inasmuch as the condition is usually compatible with relative longevity, the further indications for operation will depend upon the operative risk.» In our experience (Crafoord, pers. comm.) the prognosis in coarctation of the aorta is by no means so good as pointed out by the author. Therefore we mean that an operation should be performed in most cases.

The last part of the book is concerned with therapy. Prescriptions given in the chapter »General Medical Care» are extremely sound and intelligent. The author says that »patients with congenital malformations of the heart must learn to live with their condition, their lives should be as nearly normal as possible. Education is important and the child should be encouraged to attend regular classes». Chapter 27 is titled »Medical Aspects of the Surgical Correction of Congenital Pulmonary Stenosis or Atresia». Here is given a comprehensive report of the pre- and postoperative care in cases which are due to the Blalock-Taussig operation. Dr. Edward Park has written the foreword of the book. He says, »The success of the operation has been of great importance not only to the afflicted children but also to Dr. Taussig, for it has given her studies a practical usefulness which was not anticipated.»

Dr. Taussig's book will be of the greatest practical use to all doctors and in all clinics where there is a special interest in the diagnosis of congenital malformations of the heart. The ref. hopes that the author will have time enough in the future to give us her figures on the distribution of the various heart defects. This will increase the value of her work for these figures will tell us not only the benefit of the different operations but also the distribution regarding many other details. Without this additional material it is difficult to know which of the defects described in her book are common and which should be looked upon as pure rarities.

Edgar Mannheimer, M. D.
Stockholm, Sweden.

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A. LICHTENSTEIN

KRONPRINCESSAN LOVISAS BARNJUKHUS
STOCKHOLM

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Über Encephalitis postvaccinalis.

Von

CORNELIA DE LANGE, Amsterdam.

Bekanntlich hat die Encephalitis postvaccinalis, die seit 1925 in Frequenz zugenommen hat, die Neigung zu bestimmten Zeiten und in bestimmten Bezirken in Form kleiner Epidemien aufzutreten. Um nur einige Beispiele zu nennen: in *Kufstein*¹ erkrankten 7 Kinder 8—14 Tage nach der Impfung an Encephalitis; drei davon starben. Mit der gleichen Lymphe wurden ausserhalb *Kufsteins* 26 000 Kinder geimpft, ohne dass sich etwas ungewöhnliches zeigte. In den Jahren 1944—1945 beobachtete man im Kanton *Basel* (Schweiz) 15 Fälle (THEODOR MÜLLER²). Im Kanton *Bern* wurde in 1940 die Impfung obligatorisch gestellt; in den ersten Jahren sah man keine Encephalitis, in 1944 kam ein Fall zur Beobachtung, in 1945 fünf und in 1946 zwei Fälle (OESCH³).

In der niederländischen Provinz *Noord-Brabant* kamen im Frühsommer 1947 zahlreiche Fälle vor — es wurde dort obligatorisch geimpft wegen eines Pockenfalles im benachbarten belgischen *Luik*. Im St. Elisabeth-Krankenhaus in *Tilburg*, in dieser Provinz gelegen, wurden 26 Kinder mit dieser Diagnose aufgenommen, alle herkunftig aus *Tilburg* oder nächster Umgebung. Es handelte sich bei allen um Primo-Vaccination. In zwei Fällen könnte ein geringer Zweifel an der Diagnose bestehen. Das Alter der Kinder wechselte von 6—16 Jahren, die Inkubationsdauer

¹ Diskussionsbemerkung von F. HAMBURGER, Monatsschrift für Kinderhk. 44. 227. 1929.

² THEODOR MÜLLER, Schweizerische Med. Wochenschrift 19 Oktober 1946

³ F. OESCH. Annales Paediatrici 169. 125. 1947.

der Krankheit von 7—17 Tagen. Drei der betroffenen Kinder waren von Anfang an geistig etwas zurückgeblieben. Im Krankenhaus kamen zwei letale Fälle vor, in einer Anstalt in der Stadt noch ein dritter. Diese Tilburger Epidemie ist klinisch vortrefflich beobachtet und beschrieben worden von Dr. J. L. KEYZER¹, der Prof. B. BROUWER und mir die Gelegenheit bot, auf seiner Abteilung alle Patientchen zu sehen (4. Juni 1947). Bei allen wurde u. a. eine Blutuntersuchung vorgenommen, meines Wissens war dies das erste Mal, dass systematische Blutuntersuchungen bei einer Epidemie von Encephalitis nach Impfung vorgenommen worden sind.

Zweimal waren zwei Kinder aus derselben Familie betroffen.

Ausser den *Tilburger* Fällen erkrankten noch zwei Kinder in 's *Hertogenbosch* (Hauptstadt der Provinz *Noord-Brabant*), zwei in *Helmond* und 8 in *Breda* und Umgebung, alles Städte die ebenfalls in dieser Provinz gelegen sind.

Alle Kinder, welche wir in *Tilburg* zu sehen Gelegenheit hatten, waren mit Kuhpockenlymphe vom *Amsterdamer* Vaccinationsbureau geimpft worden. Die Reaktion auf die Impfung war eine sehr ausgiebige, sowohl örtlich wie auch im Allgemeinbefinden der Kinder.

Fall I. Die klinischen Data und das Gehirn dieses Kindes verdanke ich Dr. J. M. SOETERS, Kinderarzt in Breda. Das Mädchen *J. P.*, geboren am 13.11.1941, wohnte im Dorfe *Fynaart* in der Nähe *Bredas*. Impfung am 20.5.1947. Sie ist das zwölfte Kind aus der Kinderreihe und kongenital blind. Aller Wahrscheinlichkeit nach hatte die Mutter in dieser Schwangerschaft Rubeolae durchgemacht. Das Kind wurde ohne Erfolg von einem Augenarzt operiert. Am Nachmittag des 26. Mai erkrankt das Kind, die Temperatur ist 38.5°, nach einer Weile 40°. Es kommen Konvulsionen hinzu. Am Abend wird eine Lumbalpunktion vorgenommen. NONNESche und PANDYSche Reaktion negativ. Zellen 7/3. Eiweiss ± 14 mgr. % Wenige Minuten vor Mitternacht des gleichen Tages stirbt das Kind.

Hier betrug die Inkubationsperiode nur 6 Tage, die Dauer der Krankheit nur 1 Tag. Auffallend ist des weiteren, dass Konvulsionen vorkamen, die sonst nur bei Säuglingen beobachtet werden, was auch aus den *Tilburger* Beobachtungen hervorgeht, wo Konvulsionen kein einziges Mal

¹ J. L. KEYZER und P. P. M. NIEWENHUIS. Ned. Maandschrift v. Kinder-geneskunde. 1947. Dez. Heft.

beobachtet wurden. Die Zellenzahl im Liquor bei J. P. war auffallend gering.

Makroskopische Untersuchung des Gehirns. An der Konvexität zeigt sich eine leichte Trübung der Pia und Hyperämie. Mit dem unbewaffneten Auge ist keine Meningitis zu entdecken. Das Nachhirn wird in der gebräuchlichen Weise durch die Pedes Pedunculi abgeschnitten und das Gehirn an vertiko-frontalen Schnitten weiter betrachtet, wobei nichts auffallendes bemerkt wird. Die Tractus und Nervi optici, wie auch das Chiasma sehen normal aus; dieselben werden jedoch an Serienschnitten zerlegt werden, weil das Kind kongenital blind war und die Mutter in der Schwangerschaft Rubeolae durchmachte.

Technik der mikroskopischen Untersuchung. Aus dem Gehirn wurden mehrere Stückchen genommen und teilweise in Paraffin eingebettet zur Färbung mit Hämatoxylin-Eosin und Kresylviolett, teilweise in Zellodiu zur Färbung nach WEIGERT-PAL und VAN GIESON. Dicke der letzteren Schnitte 30 μ , der ersteren 10 bis 15 μ .

Das Resultat der mikroskopischen Untersuchung lässt sich wie folgt zusammenfassen. Die Pia mater ist hyperämisch, die Gefässe sind überfüllt und erweitert. Es lässt sich kein Entzündungsprozess feststellen, nur stellenweise sind die uninucleären Elemente in der weichen Hirnhaut um ein wenig vermehrt, polynucleäre Leukozyten finden sich nicht; das gleiche gilt für den übrigen Hirnbefund. Stellenweise ein wenig Oedem in den Maschen der Pia. Vom ganzen Pallium sind Rinde und Rindemark hyperämisch. Sehr vereinzelt findet sich im Mark ein Gefäss mit leichter uninucleärer Infiltration der Wand, auch lassen sich einige wenige Gefässe auffinden mit einem schmalen peri-adventitiellen Zellsaum. Einmal war nur auf einer Seite des Gefässes ein kleines Zellkläppchen anwesend. Dies waren also sehr geringfügige Veränderungen neben der starken Hyperämie. Im Zentrum semiovale war die Hyperämie viel weniger ausgesprochen, das gleiche gilt vom Striatum und Thalamus opticus, Nucleus ruber und Corpus subthalamicum. Besonders stark mit Blut überfüllt und erweitert, einschliesslich der kleinsten Kapillaren, waren die oberen Oliven. Der dorsale Teil der Medulla oblongata erwies sich etwas weniger hyperämisch als der ventrale. Die Nervenzellen zeigten sich überall im Gehirn gut erhalten, nur waren vereinzelt die Dendriten zu lange verfolgbar. Vereinzelte Olivenzellen waren vielleicht in geringem Masse geschwollen.

Im Kleinhirn fanden sich in der Pia erweiterte, überfüllte Gefässe. Die Purkinjezellen waren etwas geschwollen und hatten ihr Tigroid verloren. Das Zerebellum selber war leicht hyperämisch. Auch das Zervikalmark war mehr hyperämisch als normaliter.

Auf zwei Sachen muss besonders die Aufmerksamkeit gelenkt werden: erstens, dass sich im ganzen Gehirn keine Spur von Entmarkung nachweisen liess; zweitens, dass die genaue Untersuchung der Tractus

et nervi optici und des Chiasmas nur einen normalen Befund zeigten. In diesem Fall lag also wahrscheinlich die Ursache der kongenitalen Blindung des Kindes nach Schwangerschaftsrubeolae der Mutter näher peripher.

Der Gehirnprozess nach der Impfung ist hier offenbar so prodromant toxisch verlaufen, dass keine Zeit war zur Ausbildung der sonst typischen Merkmale der Encephalitis postvaccinalis, nämlich der perivaskulären Glia-Ausbreitung in das nervöse Parenchym und der Entmarkung. Wäre dieses Gehirn ausserhalb einer Epidemie zur Untersuchung gekommen, so wäre eine Diagnose einer Encephalitis postvaccinalis wohl nicht möglich gewesen; Hyperämie und geringe Veränderungen an den empfindlichen PURKINJE-Zellen können sich ja bei jeder heftigen Infektion einstellen. Dennoch gehört dieser Frühfall m. E. gewiss zur Epidemie und man täte den Tatsachen Gewalt an, wollte man nach einer anderen Diagnose fahnden. Dazu kommt noch, dass unser Fall I histologisch mit den Frühfällen DÖRINGS¹ zu vergleichen ist.

Ich hatte mir vorgestellt, dass unser erster Fall vielleicht Argumente beibringen könnte zu einer Lösung der noch strittigen Frage, ob bei Impf-Encephalitis das Primäre die Entmarkung oder die perivaskuläre Glia-Abwehr sei. Darin wurde ich jedoch enttäuscht, da beide Merkmale noch fehlten. Zweitens (und beides gilt auch für Encephalitis nach Pocken, nach Masern, nach Varizellen und für Encephalitis nach der Impfung bei Rabies), ob man hier zu tun hat mit einer Encephalitis oder ob es besser sei von einer Encephalopathie zu sprechen. Ich komme darauf nach Mitteilung der beiden anderen Fälle noch zurück.

Wohl möchte ich hier die Frage berühren, was denn eigentlich die Inkubationsdauer einer Krankheit sei. Man nimmt gewöhnlich an, dass sei die Zeit, deren das anfallende Agens bedarf, um die Anfallsstärke (und den Kampfplatz?) zu erreichen. Das Inkubationsstadium der verschiedenen Infektionen wechselt im Ganzen nur innerhalb ziemlich enger Grenzen, zeigt jedoch gelegentlich nicht unbedeutende Variationen vom normalen Verlauf. Bei Windpocken z. B. sah ich zu wiederholten Malen eine Inkubation von 3 Wochen oder länger. Ist jetzt anzunehmen, dass ausnahmsweise weniger vom

¹ G. DÖRING, D. Zf. Nervenhk. 152. 73. 1941.

schädlichen Agens eingedrungen sei, so dass es länger als sonst währt bis die Anfallsstärke erreicht ist? Eine andere Auffassung ist folgende: Das in den Körper eingedrungene Agens muss, bevor es das Gehirn angreifen kann, selber einen Entwicklungszyklus durchmachen und kann den Anfall erst dann beginnen wenn dieser Zyklus vollendet ist. Es wäre möglich, dass während eines solchen Entwicklungszyklus Mutationen eintreten von ausserordentlicher Virulenz und massenhaft Toxinen produzierend, welche Mutationen dann das Gehirn angreifen.

Dass die Impfung einen Allgemeinprozess im Körper zeitigt, geht daraus hervor, dass das Vaccinia-virus in einem grossen Teil der Fälle zwischen dem 3.—10. Tag (meist zwischen dem 6.—8. Tag) im Blute auffindbar ist.¹ Bei Encephalitis postvaccinalis hat man es wiederholt im Liquor festgestellt. Später wurden einige Fälle bekannt gegeben mit positiven Liquorbefund und ohne Encephalitis.

Fall II. Auch in diesem Fall verdanke ich die klinischen Data und das Gehirn Dr. J. M. SOETERS, Kinderarzt in Breda. *Wilhelma Br.*, wohnhaft in *Hoeven*, einem Dorf in der Nähe *Bredas*, geboren am 9. Februar 1938, wurde erstmalig am 3. Mai 1947 geimpft. Die Symptome einer Encephalitis fingen am 14. Mai 1947 an, der Exitus erfolgte am 25. Mai 1947. Also, das Kind war 9 Jahre alt, die Inkubation währte 11 Tage und die Krankheitsdauer betrug 9 Tage.

W. entstammte einer Familie mit 7 Kindern und war als junges Kind nie krank. Sie hatte jedoch Klumpfüsse, welche zweimal operiert wurden. Ein Brüderchen ist im Alter von 4 Wochen an *Spina bifida* gestorben. Ein anderer Bruder von W. wurde am 30. April 1947 auch zum ersten Male geimpft, bei ihm war die Hautreaktion viel stärker als beim Mädchen, er war aber nur einen Tag leicht unwohl. Am Abend des 13. Mai besuchte das Mädchen die Kirche, bei ihrer Rückkehr klagte sie über Kältegefühl und hatte einen Schüttelfrost. Sie legte sich ins Bett, schlief unruhig und klagte über Kopfschmerzen. Am Morgen des 14. Mai Erbrechen; nach \pm 13 Uhr mittags sprach sie nicht mehr, sondern wimmerte nur. Sie war komatös, es gelang jedoch noch, ihr einige Esslöffel Flüssigkeit einzuflössen. Sie hielt die Zehen steif und den Kopf hintenüber. Der Nacken war schmerzhaft. Temperatur am Nachmittag 39.5°, am Abend 40.8°.

Bei der Krankenhausaufnahme fand man ein schwer krankes Mäd-

¹ A. ECKSTEIN, H. HERZBERG-KREMMER, K. HERZBERG. D. med. Wochenschrift 1930. No. 7.

chen im Koma mit hohem Fieber. Das Koma hat sich bis zu Ende erhalten. Temperatur und Puls waren hoch während der ersten Tage, die Temperatur sank danach bis zur Norm herab; die Pulszahl blieb erhöht, sei es auch weniger hochgradig als im Anfang. Am 20. Mai erhob sich die Temperatur aufs Neue bis zu einer prämortalen Höhe von 41.4 bei einer Pulsfrequenz von 170.

Bei der Krankenhausaufnahme zeigten sich drei gut entwickelte Impfpusteln. Die Harnblase war überfüllt. Beiderseits war der Knie-sehnenreflex aufgehoben, ebenso der rechte Achillessehnenreflex. Beiderseits BABINSKISCHER Reflex und leichter Klonus des linken Fusses. Die Bauchreflexe waren sehr niedrig, die Bicepsreflexe positiv, beiderseits gleich. Es gab ein Zahnradphänomen. Der KERNIGSCHE Reflex war zweifelhaft, der BRUDZINSKISCHE negativ.

Im Harn gab es eine schwach positive Eiweissreaktion, mikroskopisch zahlreiche Leukozyten. Im Liquor cerebrospinalis schwach positive Reaktionen von PANDY und NONNE; 434 Zellen pro cMm. Glukosegehalt 93 mgr %, Eiweissgehalt 18 mgr %.

Am 19. Mai wurde die Lumbalpunktion wiederholt; NONNES Reaktion negativ. PANDY eine Spur. Zellen 7 pro cMm, Glukose 84 mgr %.

Das Mädchen blieb immerhin komatös und wegen Harnverhaltung¹ musste jedes Mal katheterisiert werden. Eine Blutuntersuchung am 21. Mai ergab folgendes: Hämoglobingehalt 94 %, weisse Blutkörperchen 8 900. Differentialzählung: Bas: 2. Eos 1, Stabk. 5, Segmentk. 67, Ly 21, Monozyten 4.

Es ging dem Kinde immer schlechter; der Exitus kommt am 25. Mai.

Als Therapeutica waren gegeben worden: 2 × Rekonvalescentenserum, Acidum salicylicum und Cibazol.

In diesem klinischen Bilde fehlten auch wieder die Konvulsionen. Auffallend ist die hochgradige Harnverhaltung. Die zahlreichen Leukozyten im Harn stehen aller Wahrscheinlichkeit nach nicht im Zusammenhang mit dem Krankheitsbild, sondern rührten wohl von einer chronischen Pyurie her.

Makroskopische Untersuchung des Gehirns. Das Cerebrum macht einen massiven Eindruck, obgleich das Gewicht von 1 454 Gr. nur ein Plus von zirka 100 Gr. beträgt (normales Durchschnittsgewicht in diesem Alter 1 360 Gr. (RÖSSLE und ROULET²). An der Basis lässt sich keine Meningitis feststellen, frontal basal jedoch zeigt sich eine leichte Verfärbung, während im oberen Teil der Hämisphere die Häute etwas getrübt aussehen. Sulci und Gyri sind normal konfiguriert, die Gefässe sind nicht besonders stark gefüllt. Das Nachhirn wird durch die Pedes

¹ Harnverhaltung wurde in dieser Epidemie des öfteren beobachtet, auch in Fällen, die zur Heilung kamen.

² Nach J. Brock c. s. Biologische Daten für den Kinderarzt. Berlin. J. Springer 1934.

Pedunculi abgeschnitten, der Aq. Sylvii ist nicht erweitert. Des weiteren wird das Gehirn in vertiko-frontale Schnitte zerteilt, wobei sich nichts Besonderes zeigt, namentlich sind die Ventrikel nicht erweitert.

Technik der mikroskopischen Untersuchung. Zahlreiche Stücke werden ausgeschnitten, teilweise zur Einbettung in Paraffin und Färbung nach NISL und mit Hämatoxylin Eosin, teilweise zur Einbettung in Zelloidin und Färbung der Schnitte abwechselnd nach WEIGERT-PAL und VAN GIEON.

Mikroskopische Untersuchung. Linker Gyrus frontalis + Pia. Es besteht hier nur eine mässige Hyperämie. Um vereinzelte Gefässe im Rindenmark und ausnahmsweise um ein Rindengefässchen sieht man eine Lichtung des Parenchyms zugleich mit einer mässigen Gliaproduktion. Man hat hier offenbar mit einem mehr jugendlichen Stadium des Prozesses zu tun als bei der dichteren peri-vaskulären Gliainfiltration, die später kommt. Auch fällt es auf, dass ein Teil der infiltrierenden Zellen einen breiteren Protoplasmasaum hat als die Mikroglia. Polynucleäre Leukozyten gibt es darin nicht. Ein einzelntes Gefäss weist in der Wand eine leichte Infiltration mit einkernigen Elementen auf. Ich möchte diese histologischen Bilder in der Folge eine Kombination von Rarefikation und Infiltration nennen (R—J).

Rechter Gyrus frontalis I. Die Gewebshyperämie ist hier nur eine mässige. Im Mark finden sich vereinzelte Gefässe umgeben von einer Rarefikation — Infiltrationszone.

Rechter Gyrus frontalis II mit Pia. Die Pia ist hyperämisch, jedoch nicht entzündet, in Rinde und Mark zahlreiche überfüllte Kapillare und kleine Venae.

Linkes Frontalhirn mit Centrum semi-ovale. Markscheidenpräparat und van Giesonfärbung. Mehrere Gefässe zeigen hier einen peri-vaskulären Gliasaum, andere perivaskuläre retikuläre oder schwarmförmige Ausbreitung der Glia in dichter Infiltration, jedoch auch die R—J-Form. Im Markscheidenpräparat sieht man in diesen beiden Stadien des Prozesses bereits Entmarkung. Das rechte Centrum semi-ovale erscheint weniger angegriffen als das linke.

Rechte motorische Zone. Mässige Hyperämie von Rinde und Mark. Die Betz'schen Zellen lassen sich nachweisen, sind aber nicht auffallend gross. Im Rindenmark vereinzelte R—J-Stellen und Gefässe mit Gliasäumen.

Linker Gyrus centralis post. Hier gibt es zahlreiche R—J-Stellen und es ist deutlich, dass die Zellen hier wenigstens teilweise einen breiteren Gliasaum aufweisen als die Mikroglia der dichteren Infiltration. Es lassen sich keine Körnchenzellen nachweisen. (Abb. 1.)

Rechter Gyrus parietalis sup + Pia. Hier ist stellenweise die Glia stark betroffen. Neben der Hyperämie sieht man diffuse Zellenanhäufungen, meist uninukleärer Elemente, mit wenig Protoplasma, aber

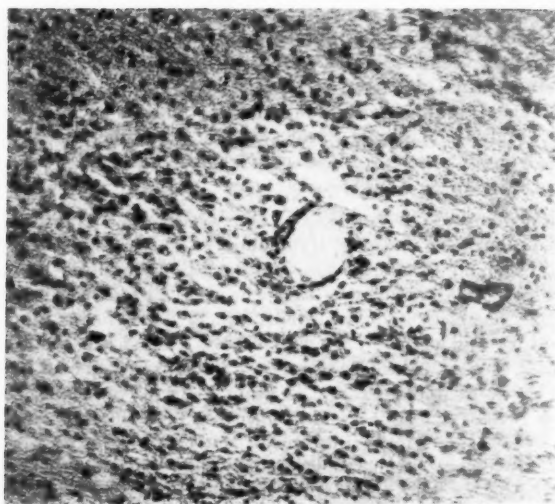


Abb. 1. Rarefikation-Infiltration Stelle im Linken Gyrus centralis post.
Färbung mit Hämatoxylin-Eosin.

auch gelappt-kernige mit breiterem Protoplasmasaum. Es findet sich ein ganz vereinzelter polynukleärer Leukozyt. Im Mark und Rinde viele kleine erweiterte und überfüllte Gefässe ohne R—J. Vereinzelte zeigen einen perivaskulären Streifen von Glia.

Rechter Gyrus temporalis II + Pia. Die Pia ist hyperämisch, Mark und Rinde nicht nennenswert. Ein vereinzelt kleines Markgefäss ist von einem R—J-Bezirk ohne grössere Zellformen umgeben.

Linker Gyrus occipitalis primus. Hyperämische Pia, auch in Rinde und Rindenmark überfüllte Gefässe, keine sonstigen Gefässreaktionen.

Nucleus caudatus. Keine blutüberfüllten Gefässe, aber unter dem Ventrikelependym befinden sich ein paar Venen mit retikulärer Glia-Ausbreitung, also das reifere Stadium des Prozesses.

Das *Putamen* ist ziemlich stark ergriffen, zeigt histologisch die reiferen Bilder.

L. Thalamus opticus. Das Gewebe ist wenig hyperämisch, zeigt aber zahlreiche R—J-Stellen. Vereinzelt Gefässe darin haben eine Wandinfiltration mit uninukleären Elementen und eine retikuläre Glia Ausbreitung, andere haben nur Wandinfiltration und keine retikuläre Glia-Ausbreitung. Es findet sich eine Ganglionzelle mit Neuronophagie.

R. Thalamus opticus. Im Markscheidenpräparat zahlreiche Ent-

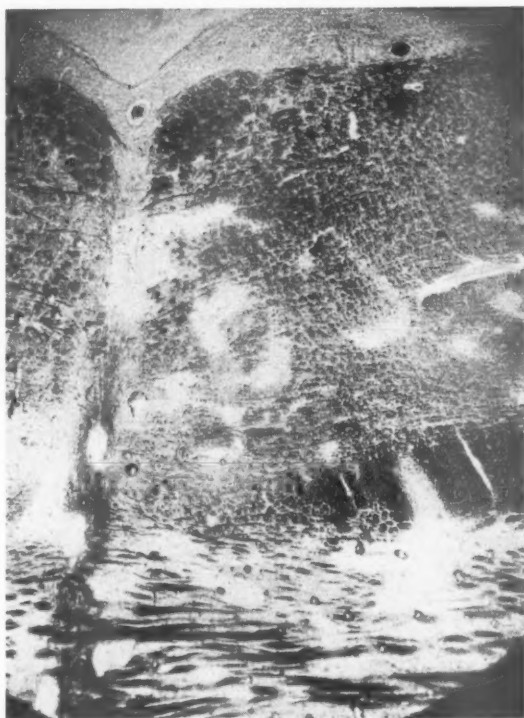


Abb. 2. Starke Entmarkung in Tegmentum und Pons. Färbung nach WEIGERT-PAL.

markungsstellen, die Gliareaktion scheint weniger intensiv, so dass man den Eindruck haben könnte, die Entmarkung gehe hier voran. In einem Präparat aber finden sich zwei Gefässe, die sowohl im WEIGERT-PAL-Präparat als auch in der anschliessenden van GIESON-coupe schon makroskopisch sichtbar sind. Das eine Gefäss zeigt weder Entmarkung noch Gliareaktion, das andere keine Demyelinisation, auf der einen Seite aber eine leichte Gliareaktion.

Gegend der unteren Oliven. Diese Schnitte sind nicht besonders hyperämisch. Die Olivenzellen sind geschont. Im Olivenareal finden sich Gefässchen mit retikulärer Gliareaktion, welche letztere aber lateral und dorsal vom Areal viel ausgiebiger ist. Stellenweise gibt es eine leichte



Abb. 3. Grosse Vergrößerung einer entmarkten Stelle mit zahlreichen Myelinkugeln. Färbung nach WEIGERT-PAL.

Randgliose. Zahlreiche Entmarkungsstellen, besonders im Gebiete des medialen Lemniscus und im Tegmentum, die Gehirnnervenkerne berührend, aber dieselben schonend. Im linken Corpus restiforme zeigt sich eine entmarkte Stelle, wo auch die Gliareaktion deutlich ist.

Schnitt durch Pons und Tegmentum. Auffallend starke Reaktionen. Die Entmarkung ist sehr ausgeprägt, die Raphe ist in ihrem Verlauf unterbrochen, der mediale Lemniscus stark angegriffen. Im Durchschnitt der Pyramidebahnen zeigen sich demyelinisierte Stellen (Abb. 2 und 3). Vereinzelte Gefässe mit Wandinfiltration und mit Zellen im peri-adventitiellen Raum. In diesem Gehirnteil scheint die Intensität von Entmarkung und Gliareaktion parallel zu gehen.

Das *Zerebellum* ist nicht hyperämisch und zeigt fast keine Beteiligung am Prozess, nur am äusseren Rande des Vliesses gibt es ein paar kleine Stellen mit Entmarkung und retikulärer Gliareaktion. Die Zellen des *nucleus dentatus* sind intakt. Das Tigroid in den *PURKINJE*-Zellen ist erhalten, ist aber nicht so schön wie normaliter.

Halsmark. Es gibt eine Randgliose um die *Fissura anterior* und um zwei Extraspalten, die sich an der Vorderseite des Rückenmarks befinden, ebenso um die *GOLLS*-schen und *BURDACH*-schen Stränge. Die Nervenzellen sind intakt. Man sieht hier mehr das R—J-Type als das reifere Stadium. Am Anfang des linken Vorderhorns und an der Peripherie beim *Funiculus BURDACHI* gibt es eine deutliche Entmarkungsstelle; dort hat die Gliareaktion den Charakter des reiferen Prozesses.

Zusammenfassend lässt sich folgendes über Fall II sagen: Die Hyperämie war bedeutend geringer als im vorigen, foudroyant verlaufenden Fall. Ein lokaler Entzündungsprozess zeigte die Pia über dem *Lobus parietalis superior*, ohne dass Gefässkragen anwesend waren. In den untersuchten Gehirnteilen fand sich stellenweise das frühe Stadium des Prozesses, stellenweise das reifere. Öfters waren im selben Gewebsschnitt zugleich beide Stadia zu beobachten und als Zeichen des frühen Stadiums dann und wann auch Gefässwandinfiltrationen. Man hatte den Eindruck, dass der Prozess frontal-kaudal an Intensität zunahm; dagegen war der Prozess im Halsmark offenbar jünger als in Pons und Tegmentum. Man bekam den Eindruck, dass die Lichtungen (R—J-Stellen) nicht immer übereinstimmten mit Entmarkungsstellen. Als die Gliareaktion dichter wird, verschwinden die Lichtungen. Auch *DÖRING* hat eine Lichtung um die Gefässe herum als Frühsymptom beschrieben. Etwas auffallendes waren an den rarefizierten Stellen die grösseren Zellformen mit breiterem Protoplasmasaum. Körnchenzellen wurden nicht beobachtet. Retikuläre oder schwarmförmige Glia-Ausbreitung und Entmarkung schienen im Ganzen parallel zu verlaufen.

Fall III. Die klinischen Data verdanke ich Dr. J. L. KEYZER in Tübing.

Das Mädchen *E. S.* wurde am 25. Dezember 1938 als viertes Kind gesunder Eltern geboren. Das erste Kind starb im Alter von vier Wochen. Das zweite, zur Zeit 14 Jahre alt, ist nervös und leicht ablenkbar. Das dritte ist gesund und steht jetzt im 13. Lebensjahr. Dann folgen mehrere Abortus und Totgeburten, welche gefolgt werden von der Geburt von *E.*

Das Kind machte Masern, Keuchhusten, Windpocken und Mumps durch. Am 2. Mai 1947 Erstimpfung, nach 6 Tagen Fieber infolge der sich entwickelnden Pusteln. Am 14. Mai wurde sie unwohl und hatte Nackenschmerzen; am 15. Mai war das Bewusstsein etwas getrübt und sie sprach eigentümlich, konnte sich nicht mehr aufrichten und auch nicht mehr gehen. Die Arme waren gut beweglich. Seit dem Abend des 14. Mai gab es Harnverhaltung.

Bei der Krankenhausaufnahme zeigte sich das Bewusstsein nur leicht getrübt. Das Mädchen wurde kurzatmig, zeigte Nasenflügelatmung, sprach sehr undeutlich und verschluckte sich. Es gibt Akrocyanose. Die Pupillen reagieren normal, die Zunge ist belegt. Herz und Lungen ohne pathologischen Befund. Der Bauch ist eingezogen, mit Ausnahme einer stark hervorstehenden Harnblase, die Nabelhöhe erreicht. Arm- und Fusssohlenreflexe sind normal, Knie- und Achillessehnenreflexe lebhaft. KERNIGScher und BRUDZINSKIScher Reflex positiv. Am Abend trübte sich das Bewusstsein mehr, das Patientchen ist jedoch noch ansprechbar. An diesem Tage erfolgte zweimal Erbrechen. Am nächsten Tage ist das Mädchen vollkommen komatös. Stockende Atmung. Der Zustand verschlechtert sich schnell. Das Fieber erhebt sich am Abend des 16. Mai bis zu 41.3° und am 17. Mai starb das Kind morgens um 7 Uhr unter Erscheinungen der Ateminsuffizienz.

Bei der Lumbalpunktion, die am 15. Mai vorgenommen wurde, fand sich heller Liquor, in der normalen Weise abfließend, vor.

NONNES und PANDYS Reaktionen positiv, Zellen 656/3 per mM3 (Lymphozyten). Glukose 79 % mgr. Total Eiweiss 63 % mgr. Liquorkurven stark pathologisch. Im Liquor WASSERMANN'S Reaktion negativ, MEINECKES positiv.

Die Blutuntersuchung ergab: Hämoglobin Sahli 88 %, Leukozyten 7 000. Formel: Eos. o. Stabk. o. Segmentk. 71, Lymphocyten 26, Monocyten 3 %. Die Therapie war: 40 cc Blutserum intramuskulär, von einem gleichzeitig geimpften Bruder, 2×10 Gr. Sulfas magnesiae rektal, 2 cc coramine intramuskulär, 4×15 000 E. Pencilline (als Prophylacticum gegen Pneumonie) 5 cc Lobeline, 1 Liter Hypodermoklyse.

Bei diesem $8\frac{1}{2}$ -jährigen Mädchen hat also die Inkubationsdauer der Krankheit 12 Tage betragen, die Krankheitsdauer 3 Tage. Auffallend ist der hohe Eiweissgehalt und der relativ niedrige Zuckergehalt der Spinalflüssigkeit.

Dr. VAN DER ZALM, stellvertretender Patholog-Anatom des *St. Elisabeth Krankenhauses* in Tilburg hat durch einzelne Probecoupees aus dem Mittelhirn die klinische Diagnose bestätigt, war aber so freundlich, mir die rechte Hälfte dieses Gehirns und den Bulbus zur ausführlichen Untersuchung zu überlassen.

Die makroskopische Untersuchung geschieht in der gewohnten Weise. Das Ganze ist etwas hyperämisch. Eine Meningitis lässt sich nicht nach-

weisen. Nach Entfernung des Gehirnstammes wird das Zerebrum in vertiko-frontale Schnitte zerlegt, wobei sich nichts besonderes vortut.

Technik der mikroskopischen Untersuchung. Zahlreiche Partien werden eingebettet in Paraffin zur Färbung mit Hämatoxylin-Eosin, nach NIEL und ebenso mehrere Stückchen in Zelloidin zur abwechselnden Färbung nach WEIGERT-PAL und VAN GIESON.

Mikroskopische Untersuchung. Über dem *Gyrus frontalis I* ist die Pia hyperämisch und geringgradig infiltriert mit kleinen uninukleären Elementen. Vereinzelte Zellen zeigen einen etwas breiteren Protoplasmasaum. Die Gefäße sind ohne Kragen und ohne Wandinfiltrat. Polynukleäre Leukozyten werden nicht beobachtet. Die Rindenkapillaria sind überfüllt, weniger die im Rindenmark. Es findet sich keine Gliareaktion vor.

Grosses Stück aus Frontalis I. R. (WEIGERT-PAL-VAN GIESON). Hier gibt es keine Entmarkung, jedoch viel retikuläre Glia und mehrere Gefäße mit einreihiger Wandinfiltration.

R. Gyrus frontalis II. Hier gibt es eine ziemlich starke peri-vaskuläre, retikuläre Glia-Ausbreitung. Einzelne Gefäße sind peri-adventitiell von einer Zellenreihe umgeben.

Gyrus frontalis III + Pia. (Präparate nach VAN GIESON und WEIGERT-PAL). Pia hyperämisch, im Mark ausgeprägte Demyelisationsherden. Rinde intakt. Peri-vaskuläre Glia-Ausbreitung; auch eine geringe Anzahl Gefäße mit peri-adventitiellem Zellsaum und Wandinfiltration. Es macht den Eindruck als ob die Entmarkung in dieser Gegend die Gliareaktion etwas übertrifft.

L. Gyrus temporalis I mit Pia. Überfüllte Gefäße in der Pia mit geringer diffuser Infiltration der Maschen. Zellen uninukleär; es zeigt sich jedoch ein polynukleärer Leukozyt. Rinde und Mark intakt.

R. Gyrus temporalis II. Vereinzelte kleine Entmarkungsstellen und dem Anschein nach etwas mehr peri-vaskuläre Gliareaktion.

L. Lobus parietalis sup. Hyperämische Pia mit nur sehr geringer diffuser Infiltration der Hirnhaut; auch die Rinde zeigt hier zahlreiche überfüllte kleine Gefäße. Im Marke zahlreiche Venae mit peri-vaskulärer Gliareaktion.

R. Lobus parietalis sup. Die Pia ist hyperämisch und stellenweise diffus infiltriert, sie zeigt hier und da etwas Oedem in den Maschen. Sonst findet sich in diesem Teil praktisch nichts Abweichendes (Färbung der Schnitte nach WEIGERT-PAL und VAN GIESON).

L. Occipitalis I + Pia. Rinde, Mark und Pia hyperämisch. Keine Entmarkung und nur geringe peri-vaskuläre Gliareaktion. Geringe Gefässwandinfiltration und Gefässäume.

Zentrum semi-ovale Vieussenii. Peri-vaskuläre Gliareaktion ohne Entmarkung.

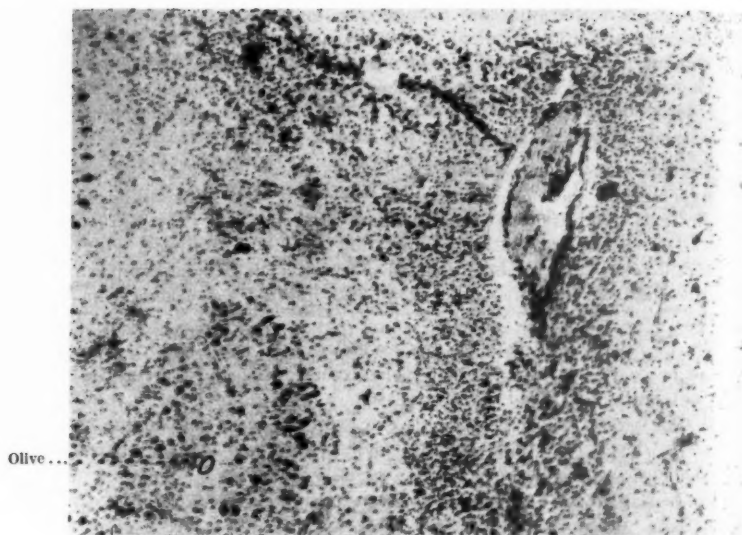


Abb. 4. Stadium der peri-vaskulären Gliareaktion. Färbung nach Nissl.

Nucleus caudatus. Vereinzelte Gefässe haben einen peri-adventitiellen Gefässsaum.

Thalamus opticus. Praktisch ohne Abweichungen, nur an einem Gefäss zeigt sich eine Gliareaktion.

Brücke. Im rechten Brückenarm befindet sich ein peri-vaskuläres Glia- und Entmarkungsherden, sonst scheint sowohl in der Brücke selbst als auch im Tegmentum die Gliareaktion öfters ohne Entmarkung vorzukommen. Die Nervenzellen sind überall geschont, stellenweise aber sieht man um ein kleines Gefäss in einem Nervenkern eine deutliche peri-vaskuläre Gliareaktion. Einzelne Gefässe haben einen peri-adventitiellen Zellsaum.

Medulla oblongata. Hier ist der ventrale Teil bedeutend stärker angegriffen als der dorsale. In ersterem findet sich viel retikuläre Glia-Ausbreitung. Stellenweise berühren sich die Plakate (Abb. 4). In den Oliven selber gibt es auch einige kleine Ausbreitungen. Es finden sich besonders im dorsalen Teil des verlängerten Marks vereinzelte kleine und grössere Venae mit einem dünnen peri-adventitiellen Zellsaum. Auch in der Medulla obl. scheint die Entmarkung weniger stark fortgeschritten zu sein als die Gliareaktion. Die Nervenzellen sind überall intakt. In der Raphe hat die Glia zugenommen. Es gibt keine Randgliose.

Oberes Zervikalmark. Keine Randgliose, auch sonst keine Abweichungen, nur in der Fissura ant. befindet sich ein Gefäss mit dünnem peri-adventitiellem Zellsaum.

Zusammenfassung.

Dieser Fall unterscheidet sich vom vorigen dadurch, dass hier das Stadium der Rarefikation fehlt. Ferner hat man den Eindruck, dass hier die Gliareaktion der Entmarkung vorangeht.

In der Histologie der Encephalitis postvaccinalis sind insbesondere die Blutgefässe (Venae) und deren Verhältnis zu Lymphozyten und Gliazellen bemerkenswert. Auf Grund eigenen Studiums und der Literatur seien folgende Bilder erwähnt: erstens als Frühsymptome ein losmaschig Werden der Gefässwand und der nächsten Umgebung, das Ausschwitzen von Plasma, die lymphozytäre Infiltration der Gefässwand, wobei sich dann und wann auch vereinzelte Plasmazellen finden, eine peri-adventitielle Umsäumung des Gefässes mit uninukleären Elementen (Lymphozyten?), meistens nur eine Zellreihe breit, eine Häufung uninukleärer Elemente dann und wann gemischt mit roten Blutkörperchen im VIRCHOW-ROBINSchen Raum. Letztere waren in meinen Präparaten öfters auffallend weit, vielleicht, wenigstens teilweise, zu betrachten als Kunstprodukt infolge der Härtung der Gewebstückchen. Im folgenden Stadium kommt es in den gelichteten Partien um die Gefässe zu einer mässigen Glia-Ausbreitung. Körnchenzellen findet man dort nicht, wohl aber sind Zellen vorhanden, die grösser sind als Mikroglia und die einen breiteren Protoplasmasaum aufweisen. Diese Stellen habe ich als Rarefikation-Infiltration Stadia bezeichnet. Dieses Stadium findet sich öfters in derselben Coupe als das nächste. Die Infiltration wird dichter, so dass die Stellen nicht mehr gelichtet erscheinen. Die Infiltration ist streng beschränkt auf das Parenchym um Venen herum. BROUWER¹ hat diese Ausbreitung eine retikuläre genannt. Man könnte auch von einer Ausbreitung in Form eines Bienenschwarms sprechen. Dann kommt auch die Entmarkung. Dabei muss man zwischen Schein und Wesen ent-

¹ B. BROUWER. Maandschrift v. Kindergeneeskunde 8. No. 10. 1939 und Annales Paediatrici 154. 121. 1939.

scheiden. Bei wirklicher Entmarkung sieht man in den WEIGERT-PAL-Präparaten peri-vaskulär runde Stellen mit einem mehr oder weniger deutlich gyrierten Rand. Dort ist das Mark der Nervenfasern destruiert und dort befinden sich zahlreiche Myelinkugeln. Beim Betrachten der Präparate mit der Lupe oder mit dem unbewaffneten Auge bekommt man den Eindruck — besonders wenn die VIRCHOW-ROBINSchen Räume weit sind — dass die Zahl der entmarkten Stellen eine viel grössere sei, als dies in der Wirklichkeit der Fall ist. Diese Scheinentmarkungen sind scharf begrenzt, nicht gyriert, aber lineär dem Verlauf des Gefässes folgend oder rund, wenn das Lumen quer getroffen ist. Man sieht dort keine Myelinkugeln, aber öfters Zellhäufchen und diese Zellen befinden sich in den VIRCHOW-ROBINSchen Räumen.

Echte Entzündungskragen mit polynukleären Leukozyten (englisch: cuff, französisch: manchettes) habe ich in meinen Präparaten nicht gesehen, und auch die Literatur erwähnt dieselben nicht. Ich sah im Frühstadium einen ganz vereinzelt Leukozyt in der Pia. Bei der HEINE-MEDINSchen Krankheit ist im Anfang die Zahl der Polys eine weit grössere.

Makroskopisch hat die Impfencephalitis keinen typischen Aspekt, bisweilen ist die Hyperämie schon auffallend und die Pia stellenweise etwas getrübt.

Das pathologisch-histologische Substrat wurde anfänglich als ziemlich monoton beschrieben, und zwar als ein diffuser Prozess des ganzen Grosshirns und öfters auch das Rückenmarks, wobei die graue Substanz meistens geschont wurde und wobei sich um die Venen eine Gliareaktion manifestierte sowie eine Entmarkung. Die Achsenzyylinder wurden dabei mehr oder weniger angegriffen.

Als sich nach 1925 in Holland mehrere Fälle von Impfencephalitis ereigneten, wurden von den Holländern VAN BOUWDIJK-BASTIAANSE, BOUMAN und BOK, VAN HASSELT, BIJL und TERBURGH wichtige Untersuchungen publiziert, die grosso modo übereinstimmten mit den Befunden von TURNBULL und MC. INTOSH aus 1912, welche jedoch erst in 1926 veröffentlicht wurden.

Je nachdem auch an anderen Stellen Fälle von Impfencephalitis zur Untersuchung kamen, hat man Abweichungen von den ersten Befunden festgestellt. Es stellte sich dabei heraus, dass die

graue Substanz bisweilen stark angegriffen wird, so dass der Name »Leuco-Encephalitis«, den VERLINDE¹ noch gebraucht, nicht richtig ist. Im Falle von STURSBURG und ROTH² — ein 11-jähriges Mädchen betreffend — z. B. war insbesondere die graue Substanz der Rinde und der Stammganglien lädiert, während die Nervenzellen in der Hauptsache geschont blieben. Fälle, worin die Ganglienzellen teilweise schwer angegriffen, teilweise ganz destruiert waren, finden sich aber auch in der Literatur (z. B. OESCH³). Neben Hyperämie kann man auch Oedem finden, Nekrosen, Blutungen beginnende Thrombosen und Ausschwitzung von Plasma aus den Gefässen.

Meistens sind Gehirnstamm und verlängertes Mark nicht am stärksten angegriffen, während die Befunde am Rückenmark sehr auseinandergehen. L. SUPPAN (zitiert nach PETTE⁴) konnte feststellen, dass bei Kindern, jünger als 5 Jahre, das Mittelhirn und die Gegend um den 4. Ventrikel mehr am Prozess beteiligt waren als bei älteren und Erwachsenen. In frischen Fällen nehmen die Hirnhäute immer mehr oder weniger am Prozess teil.

Die Verbreitung durch das Gehirn ist nicht immer diffus, sondern zu wiederholten Malen herdförmig, mit grossen geschonten Arealen, so dass der Aspekt dann der multiplen Sklerose ähnlich sehen kann. PETTE (l. c.) beobachtete dies bei einem 14-jährigen Mädchen.

WOHLWILL⁵ war der erste, der bei Masernenzephalitis die Aufmerksamkeit lenkte auf das Vorkommen eines Gliaaumes um das Rückenmark herum und subependymaler Glia-schichten um den Ventrikeln. Das gleiche kann man auch öfters bei der Impfencephalitis beobachten, wo das mikroskopische Bild in so hohem Masse dem der Masernencephalitis ähnelt. Dieselbe weitgehende Übereinstimmung gilt für die Encephalitis nach Pocken und Wind-

¹ J. D. VERLINDE. De vergelijkende histopathologie van de niet etterige ontstekingen van het centrale zenuwstelsel. Verh. van het Instituut voor Praeventieve Geneeskunde te Leiden VI. 1947.

² H. STURSBURG und F. ROTH. D. med. Wochenschrift 1940. II. 962.

³ F. OESCH. Annales Paediatrici 169. Aug. 1947.

⁴ H. PETTE. Die akut entzündlichen Erkrankungen des Nervensystems. G. Thieme Verlag. Leipzig 1942.

⁵ F. WOHLWILL. Z. f. d. ges. N. u. Ps. 112. 1928.

pocken und nach Impfung gegen Rabies. Bei sehr jungen Kindern sieht man aber immer ein Keimzentrum, eine Glia-schicht, unter dem Ventrikelependym, dort ist das also ein physiologischer Reifungsprozess.

Auch sei noch erwähnt, dass einige Male in Spinalganglia- und in Rückenmarkswurzeln lymphozytäre-plasmazytäre Infiltrate beobachtet worden sind.

Anfänglich hat man gemeint, dass bestimmte Gehirnteile oder Systeme nicht oder nur in ganz beschränkter Weise in Mitteleinschaff gezogen würden. SPIELMEYER¹ meinte dies sei der Fall beim Kleinhirn, den Oliven und dem Ammonshorn. Für die Oliven gilt das gewiss nicht; auch das Zerebellum wird öfter angegriffen als man anfänglich meinte und DÖRING (l. c.) sah in einem seiner Fälle, dass überall die Ganglienzellen intakt waren, nur im Zellband des Ammonshorns fand er vereinzelte durch Ischämie geschädigte Zellen.

In älteren Fällen kann es, wie dies BROUWER, DE JONGH und ROCHAT² für echte Pocken gezeigt haben, zu einer Fibrose kommen und zur Bildung zahlreicher Astrozyten. Vielleicht könnte man hierin eine Erklärung finden für die Tatsache, dass Restsymptome einer Impfencephalitis sich öfters erst nach Jahren vortun, nämlich dass sich erst eine Narbe mit Retraktion bilden muss.

Angesichts der allgemeinen Pathologie erregen zwei Fragen Interesse. Erstens: Ist die Impfencephalitis wirklich ein Entzündungsprozess? Zweitens: Geht die Entmarkung der peri-vaskulären Gliareaktion voran oder ist das umgekehrte der Fall?

Die Definition eines Entzündungsprozesses wird von verschiedenen Pathologen in verschiedener Weise gestellt. DÖRING (l. c.) konnte zwei Fälle von Impfencephalitis mit sehr kurzer Krankheitsdauer untersuchen. Er fand dabei eine lymphozytäre Gefäßwandinfiltration und eine saumförmige peri-adventitielle Ausbreitung von Lymphozyten. Auf Grund dieser Befunde will er den Prozess eine Entzündung nennen. In einem späteren Stadium

¹ W. SPIELMEYER. *Monatsschrift f. Kinderhk.* 44. 195. 1929.

² B. BROUWER. C. L. DE JONGH. R. R. ROCHAT. *D. Z. f. Nervenhk.* 131. I. 1933.

ändert sich das Bild. Auch in unserem ersten Fall fand ich die durch DÖRING beschriebenen Abweichungen, sei es auch nur in sehr bescheidenem Masse. Wichtig ist, dass in den Fällen von Impfenzecephalitis, wo eine Blutuntersuchung vorgenommen wurde, nie eine Entzündungsreaktion gefunden wurde, und dass der Liquor cerebrospinalis höchstens einen ganz vereinzelt Leukozyt enthielt, meistens aber nur einkernige Elemente. Dies steht stark im Gegensatz zur HEINE-MEDINSchen Krankheit, wo im Anfang regelmässig eine Leukozytose von 15—30 000 Zellen gefunden wird und wo der Liquor reichlich polynukleäre Leukozyten enthalten kann. Weiter betrifft der Prozess nicht ausschliesslich die Venae, obgleich diese im Vordergrund stehen, und schliesslich gibt es in der weissen Substanz bei der HEINE-MEDINSchen Krankheit Gliaknötchen ohne Zusammenhang mit einem Gefäss.

Was die zweite Frage betrifft: die Mehrheit der Untersucher — bei uns auch B. BROUWER — neigen dazu, die Entmarkung als der Gliareaktion vorangehend zu betrachten. Aus SPIELMEYERS Beschreibung seiner Befunde bekommt man den Eindruck, dass nur Präparate nach NISSL gemacht worden sind. Bei seinen eigenen Untersuchungen spricht er nicht über Entmarkung und erwähnt dieselbe nur beiläufig in den Arbeiten anderer. Über die Glia sagt er: perivenöse und Randproliferation der Glia ist das Haupt symptom. Dieselbe ist das Produkt einer direkten, funktionellen Reizung der Glia und zu betrachten als eine Abwehrreaktion. Der schädliche Stoff tritt aus den Venen aus.

Die zwei foudroyanten Fälle, die DÖRING beobachten konnte, haben ihn und mit ihm PETTE dazu gebracht, die Gliareaktion als die vorangehende zu betrachten. DÖRINGS erster Fall betraf einen 15 Monate alten Knaben, der zehn Tage vor dem Tode zum ersten Male geimpft wurde; 7 Tage später erkrankte er und nach weiteren 2 Tagen, also am 9. Tage post vaccinationem, wurde er im Krankenhaus aufgenommen. Im Liquor fanden sich 74/3 Zellen. Am nächsten Tage starb das Kind. Hier fehlten bei der mikroskopischen Untersuchung die Entmarkungen noch völlig. Die pialen Gefässe waren erweitert und blutüberfüllt, zeigten Wandinfiltration mit Lymphocyten; auch in einer gewissen Entfernung der Gefässe waren hier und da Lymphocyten auffindbar. DÖRING

sagte nicht, ob und in welcher Weise er die Lymphozytennatur dieser Zellen, die ja bekanntlich Mikrogliazellen sehr ähnlich sind, feststellte. Auch ich habe das bei meiner Untersuchung nicht tun können, weil die PENFIELD-Methode uns in nicht ganz frischem Material nur dubiose Resultate gegeben hat. Es ist aber sehr wahrscheinlich, dass die Zellen aus dem Frühstadium Lymphozyten sind. Auch die stark erweiterten Gefässe im Mark des Grosshirns zeigten lymphozytäre Infiltration. Es ist mir nicht deutlich, ob DÖRING sagen will: eine Infiltration der Gefässwand oder um das Gefäss herum. Buchstäblich sagt er folgendes: »Auch in der Hirnsubstanz, vor allem im Marklager des Grosshirns, zeigen die besonders stark erweiterten Gefässe eine lymphozytäre Zellinfiltration, die oft lediglich einer Gefässwandseite kappenartig aufsitzt und nur selten das ganze Gefäss einschneidet. Stellenweise hatte die äussere Gefässwand eine lockere Struktur bekommen und war eine geronnene Massa aus den Gefässen getreten. Nirgendwo gab es eine peri-vaskuläre Gliareaktion.«

Obleich PETTE offenbar in diesen Befunden eine Stütze findet für die Auffassung, dass die Gliareaktion der Entmarkung vorangeht, meine ich, dass er dazu nicht berechtigt ist, erwähnt ja DÖRING in diesem Frühstadium gar keine Gliareaktion. Die peri-vaskuläre Gliareaktion gehört zum nächsten Stadium.

Im zweiten Fall DÖRINGS handelte es sich um einen 27-jährigen Mann, der am 26. Juni 1940 revacciniert wurde; vierzehn Tage nach der Impfung wurde er tot in seinem Bett gefunden. Zuvor hatte er nur über Schmerz im linken Oberarm geklagt; am Tage vor dem Tode erklärte er, dass alles wieder in Ordnung sei und war in gewöhnlicher Weise seiner Arbeit nachgegangen. Auch hier war im Gehirn keine Entmarkung auffindbar, man sah jedoch stellenweise im Parenchym, peri-vaskulär, sehr kleine Gliawucherungen. Diese Gefässe hatten keine Wandinfiltration. Die vaskuläre Reaktion war jedoch viel ausgiebiger als die peri-vaskuläre. Offenbar ist DÖRING der Meinung zugetan, dass Gefässwandinfiltration (oder Gefässinfiltration?) nicht gleichzeitig vorkommt mit retikulärer oder schwarmförmiger Ausbreitung der Glia. Meinen Präparaten nach jedoch können retikuläre Ausbreitung und Gefässwandinfiltration wohl synchron vorkommen und gleichzeitig mit der

Anwesenheit von Zellen im VIRCHOW-ROBINSchen Raum, also peri-adventitiell.

Dieser zweite Fall DÖRINGS kann als eine Stütze betrachtet werden für die Auffassung, dass die Gliareaktion der Entmarkung vorangehe; mein dritter Fall weist auch mehr oder weniger in diese Richtung.

Zusammenfassung.

Es werden drei Fälle von Encephalitis post vaccinationem aus der *Noord-Brabantschen* Epidemie des Frühsommers von 1947 mitgeteilt. In diesen drei Fällen wurde eine ausführliche Gehirnuntersuchung vorgenommen. Einer dieser Fälle verlief foudroyant.

Mikroskopisch waren drei Stadia im Prozess der Encephalitis zu beobachten, durch ihren histologischen Charakter deutlich von einander unterscheidbar (1 Hyperämie, 2 lymphozytäre Reaktion und 3 Glia-Ausbreitung peri-vaskulär ins Parenchym mit Entmarkung). Hyperämie und lymphozytäre Reaktion können sich zusammen vorfinden. Falls gewünscht, könnte man in diesem Stadium von einem Entzündungsprozess sprechen. Das Bild ist jedoch nicht ohne weiteres mit dem der HEINE-MEDINSchen Krankheit vergleichbar. Die Untersuchung des dritten Falles gab einige Hinweise darauf, dass die Gliareaktion der Entmarkung vorangehe. Im Anfang des dritten Stadiums kann eine Lichtung mit leichter peri-vaskulärer Gliareaktion beobachtet werden.

Es gibt keine Gehirnteile, die bei der Impfencephalitis konstant geschont bleiben.

Die Benennung der Encephalitis postvaccinalis als eine Leuko-Encephalitis ist unrichtig, weil die graue Substanz öfters auch mehr oder weniger schwer geschädigt ist.

Histologische Untersuchungen erlauben nicht, sich eine Meinung darüber zu bilden, ob das Vaccinia-Virus die Ursache der Encephalitis sei, oder ob ein schon vorhandenes Virus aktiviert werde, oder schliesslich, ob hier eine Antigen-Antikörperreaktion bestehe.

Summary.

In May 1947 an epidemic of encephalitis postvaccinalis occurred in the Dutch province of *Noord Brabant*. The popu-

lation had been vaccinated on a large scale on account of a case of smallpox in the neighbouring Belgian town of *Luik*.

The author has investigated the brains of three children who died of encephalitis (after primo-vaccination). One of the cases ran a lightning course. Post mortem only hyperemia of the brain was found and a slight infiltration of some vessel-walls with uninuclear elements. This represents the first stadium of the process. As a second stadium one may regard a rarefication of the parenchyma round the bloodvessels with a slight infiltration with microglia and with cells somewhat larger with broader protoplasm than the microglial cells. In the third stadium this infiltration becomes more dense and there is demyelination. No communis opinio exists as to the fact whether the glial reaction or the demyelination comes first. The author on account of her investigation, inclines to the opinion, that it is the glial reaction. The histological pictures do not give any help in deciding the question, whether it is the vaccinia-virus itself, which is the cause of the encephalitis, or whether a latent virus in the brain is activated by the vaccination or lastly if an antigen-antibody reaction exists. Study of the literature on encephalitis following vaccination against small-pox proves that it is wrong to call the disease a leuco-encephalitis, as in several cases the grey matter also has been severely damaged. Neither is the process always diffuse. Large territories may be spared even so that the histological pictures resemble those of sclerosis multiplex. On the other hand there are no parts of the brain, which are spared in every case of encephalitis postvaccinalis.

Résumé.

En mai 1947 une épidémie d'encéphalite post-vaccinale régnait dans la province hollandaise de *Noord Brabant*. Un grand nombre des habitants avaient été vaccinés à cause d'un cas de petite vérole dans la ville voisine belge de *Luik*.

L'auteur a examiné les cerveaux de trois enfants morts d'encéphalite (après primo-vaccination). Un de ces cas avait un cours foudroyant. Post mortem on constata seulement l'hyperémie du cerveau ainsi qu'une légère infiltration des parois de quelques vaisseaux par des éléments uninucléaires. Ceci représente

le premier degré du procès. Comme second degré on peut considérer une raréfaction du parenchyme autour des vaisseaux sanguins avec une légère infiltration de microglia et avec des cellules un peu plus grandes et d'un protoplasme plus large que les cellules microgliales. Dans le troisième degré l'infiltration devient plus dense et il y a de la demyelinisation. On ne sait pas d'une manière certaine si la réaction gliale précède la demyelinisation ou vice versa. Par suite de ses observations l'auteur est d'avis que la réaction gliale se produit la première. Les faits histologiques ne facilitent d'aucune façon la réponse à la question suivante: est-ce le virus vaccinal lui-même qui est la cause de l'encéphalite, ou un virus latent dans le cerveau est-il activé par la vaccination, ou bien y a-t-il une réaction antigène-anticorps? L'étude de la littérature relative à l'encéphalite après vaccination contre la petite vérole prouve que c'est une erreur d'appeler cette maladie: leuco-encéphalite, puisque souvent la substance grise est gravement lésée aussi. Le procès n'est pas toujours diffus non plus. De grandes parties peuvent être épargnées, même de telle façon que les faits histologiques ressemblent à ceux de la sclérose multiplex. D'autre part il n'y a pas de parties du cerveau qui soient constamment préservées dans chaque cas d'encéphalite post-vaccinale.

Resumen.

En mayo de 1947 una epidemia de encefalitis postvacunal se extendió por la provincia holandesa de «Noord Brabant». La población había sido vacunada en gran escala a causa de un caso de viruela en la ciudad vecina de Luik, en Bélgica.

El autor examinó los cerebros de tres niños que fallecieron de encefalitis (después de vacunación prima). El curso de la enfermedad en uno de ellos fué rapidísimo. *Post mortem* se halló sólo hiperemia del cerebro y una pequeña infiltración de algunos vasos por elementos nucleares. Esa es la primera fase de la enfermedad. Como segunda fase se puede considerar la rarefacción de la parénquima alrededor de los vasos sanguíneos con una pequeña infiltración de microglia y con células un poco mayores y protoplasma más ancho que el de las células microgliales. En

la tercera fase la infiltración es más densa y hay desmielinación. No hay opinión general sobre si viene primero la reacción glial o la desmielinación. Las figuras histológicas no sirven para decidir la cuestión de si es el mismo virus vacunal el que ocasiona la encefalitis o si un virus latente en el cerebro es activado por la vacunación y de si existe una reacción antígeno-anticuerpo. La literatura médica sobre encefalitis subsiguiente a vacunación contra viruela comprueba que es erróneo llamar a la afección «leuco-encefalitis», en vista que en varios casos la substancia gris ha sido seriamente dañada. Tampoco el proceso es siempre difuso. Se pueden preservar grandes regiones aun que las figuras histológicas se asemejen a las de la esclerosis múltiple. Por otra parte no hay ninguna parte del cerebro que esté siempre preservada en cada caso de encefalitis postvacunal.

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FROM THE SAMARITEN CHILDREN'S HOSPITAL, STOCKHOLM
HEAD: PROFESSOR NILS MALMBERG.

Subcutaneous Administration of Amino Acids.

By

S. URWITZ, Stockholm.

Amino acid preparations have until now been used perorally in general as a supplementary nourishment for premature infants (Magnusson 1944) as also parenterally to keep bad surgical cases on nitrogen equilibrium (Lidström 1944). The curves of Magnusson show a striking increase in weight by administration of amino acids, and the curves of Lidström show that the body utilizes the injected amino acids without increasing the excretion of nitrogen in the urine.

As a consequence of the nowadays increasing number of choleraic conditions among infants parenteral administration of fluids have been widely applied during last years. Blood or serum has been given intravenously, intraossally or intraperitoneally and Ringer solution with glucose has been used intravenously or subcutaneously. We have also used an aminoacidpreparation (Aminosol¹ and Aminosol-glucose) intravenously in such cases with good effects. The possibility of compensating the very heavy protein losses by amino-acids is undoubtedly of great importance when treating these life-threatening conditions.

Injections in sinus sagittalis, a common practice in Sweden, can be used only during four or five days, but after about ten injections it is usually difficult to continue the aminosol treatment in this way. Up till now subcutaneous administration of this amino-acid preparation in man has not been tried, mainly be-

¹ Aminosol is prepared by Vitrum, Stockholm. The Aminosolsolution contains 3.3 % amino-acids and the Aminosol-glucose 3.3 % amino-acids and 5 % glucose.

cause the preparation is good substrate for bacteria. However, it seemed reasonable to try the preparation in the form of aminosol-glucose given subcutaneously. We have until now injected it in 21 children, who in total have got 240 injections i. e. 10 130 ml. We have not seen complications caused by the preparation or the mode of administration. Unfortunately we have not been able to follow the blood and urine nitrogen in our little patients.

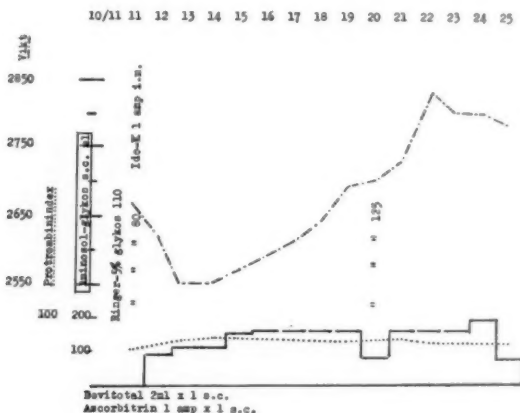


Fig. 1.

The following cases show that the subcutaneous administration of amino-acids not only makes the patients keep their weight but even increase it.

The first patient was a two days old boy, with atresia of the oesophagus (fig. 1). His weight at birth was 3 090 g. He received in 14 days 1 860 ml Aminosol-glucose. The autopsy showed only slight oedemas in the subc. tissue of the breast after the last injection. Surgical treatment had been suggested to the parents but they refused. It is probable that the administration of fluids of the same kind is important in surgical cases of this kind. Furthermore, the weight curve is interesting as compared to the curve of another case of atresia of the oesophagus (Urwitz 1946) where aminosol was given intravenously. In total 1 225 ml

of a 3.3 % aminosol solution were given during thirteen days. During the treatment the child lost 270 grams, in spite of a simultaneous supply of Ringer solution and glucose.

In another case with atresia of the bileducts and the small intestine where the bowel was quite unable to utilize the food given orally, one succeeded in keeping the weight and the general condition fairly good. During twelve days 1 265 ml were given once or twice daily in doses of 40—110 ml. The weight decreased from 2 540 to 2 470 g. *Sub finem vitae* a decrease in weight of 350 g occurred during the last 5 days in spite of 1 000 ml aminosol-glucose given subcutaneously.

Nowadays the supply of protein hydrolysates is considered to have a special importance in diseases of the liver, above all in hepatitis. It is believed that the liver is protected by the amino-acids stored in it. The following observation was unfortunately troubled by the fact that the diet was changed from boiled cow-milk to breastmilk in the beginning of the aminosol-glucose treatment.

The case was a four months old boy (fig. 2) who was admitted to the hospital 3/5 1947. He had been vomiting for 1 week, and had clay coloured stools. The Meulengracht test was 1:22. The situation was complicated by a strangulated hernia inguinalis with blood in the faeces. After reposition 4/5 nothing happened until May 19 when a large amount of ascites was discovered. The following days his condition was almost hopeless with violent vomiting and watery, discolored stools. The Meulengracht test rose to 1:42. On the 22/5 subcutaneous Aminosol-glucose-treatment began. On May 27 the ascites had almost disappeared, and the boy was in a relatively good condition. The recovery was complicated by a pharyngitis with dyspepsia. It is possible that his weight could have been raised earlier and more effectively by larger doses of aminosol-glucose. As seen from the curves, the weight is constant with a daily supply of 200 ml of aminosol-glucose, but it decreases with less.

Cholera infantum was the disease that first caused us to try the subcutaneous injections. The results of the treatment have not proved convincing, if figures only are considered. Out of

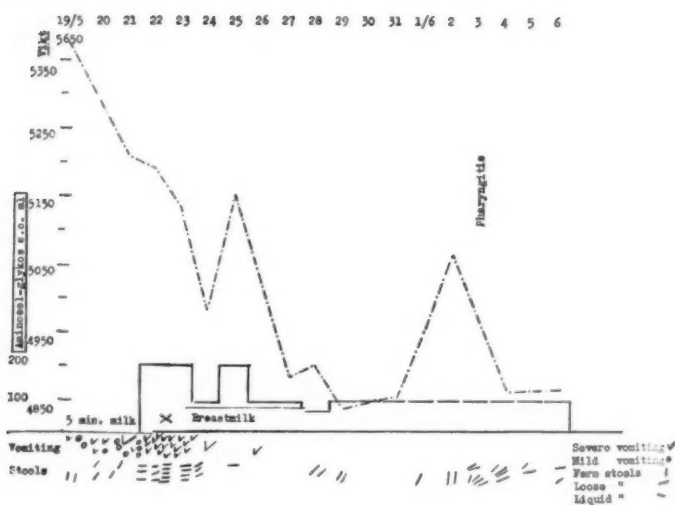


Fig. 2.

seven cases four died. This is partly due to the fact that in the beginning we did not dare to use this way of injection except in desperate cases. In our cases of cholera infantum, we have until now only given occasional injections, and it is in consequence impossible to judge about the effect from the scant material. No doubt an intense supply of fluids in the form of blood, amino-acids, Ringer solution and glucose, intravenously and subcutaneously, is the suitable way to make up for the violent losses of water, proteins and chlorides.

In other conditions with such losses through vomiting — by pylorostenosis and invaginations — aminosol-glucose given subcutaneously has been very useful. The children, generally very desiccated, have absorbed the preparation with no difficulty, and it was possible to give two injections daily. This treatment has been used in four cases of pylorostenosis, one of which was very grave, in fact a surgical case. It was a five weeks old boy, with a birthweight of 3 140 g. When admitted to the hospital his weight had decreased to 2 910 g and in spite of large doses of

spasmolytics he threw up between 300—500 gr per day. After two weeks the weight was 2 660 g. It was not until five weeks after the admittance that he ceased to vomit. He had then got in a total of 1 635 ml of aminosol-glucose in 21 injections with 40—100 ml each dose.

In two cases of invagination, which were operated, aminosol-glucose subcutaneously seemed to be beneficial. Both recovered. One of the patients had a perforation of the intestine, and it was impossible to give anything orally during five days. In addition the child got serum intrasinally and intraossally as also Ringer solution + 5 % glucose subcutaneously and intraossally.

Furthermore five subcutaneous aminosol-glucose injections were given to a boy with 30 % haemoglobin caused by *morbus haemolyticus neonatorum*. He vomited considerably and took no fluid orally. For instance, when 18 days old, he did not take more than 160 g breastmilk pro die.

We have, of course, all the time been waiting for complications such as hyperpyrexia and anaphylactic reactions, but until now we have escaped all side reactions. The quantity supplied — in ordinary cases an ampoule of 90—100 ml — was injected in two places at the same time under the cutis of back, side and breast. The bullae were generally after a couple of hours totally absorbed. The injections were not more painful than those with Ringer solution and glucose, and the fluid was absorbed equally fast.

After the supply of aminosol-glucose, we have twice noticed a rise of the temperature. These were two desiccated cases of pylorostenosis, both of which had been afebrile, when after one week they got their first aminosol-glucose injection out of the same bottle. At that time we were using bottles of 500 g which have later been abandoned. In the afternoon both children had a rise of temperature to 38° C but looked well. Three days later the same quantity was given from the same bottle without any rise of temperature. The fever can therefore not be attributed to the preparation as such, but to some other reason.

Despite the fact pointed out by Wretling (1945) with regard to guineapigs and rabbits, and by Lidström (l. c.) with regard to human beings, that aminosol has no anaphylactic powers, we

have further investigated in the matter. In a case of inoperable meningomyelocele after a pause of 16 days, another injection of 19 ml was given and a child with a severe brain injury got exactly the same quantity of aminosol-glucose subcutaneously 20 days after the first injection without the slightest reaction.

Summary.

When used subcutaneously, aminosol-glucose is an innocuous parenteral feeding, provided that the ampoule, once broken, is not used a second time. The preparation can very well replace the Ringer solution and glucose, and in consequence a protein therapy can be realised even when oral feeding is found impossible or made difficult, or when injections in veins, bone marrow and abdomen have to be spared for other purposes. We have found that the suitable quantity is 20—40 ml per kg bodyweight and day, given by 1—2 injections daily.

Résumé.

Administré par injections sous-cutanées, l'aminosol-glucose est un aliment parentérale inoffensif, pourvu que l'ampoule, une fois rompue, ne soit pas employée une seconde fois. Ce produit peut très bien remplacer la solution Ringer et la glucose et, par conséquent, une thérapie par la protéine peut être pratiquée même lorsqu'on trouve l'alimentation par la bouche impossible ou difficile, ou si les injections dans les veines, la moelle des os ou l'abdomen doivent être réservées à d'autres buts. Nous avons trouvé que la quantité convenable est de 20—40 ml par kg du poids corporel et par jour, administrée en une ou deux injections chaque jour.

Zusammenfassung.

Die subkutane Anwendung von Aminosol-Glukose ist eine unschädliche Form der parenteralen Zufuhr, vorausgesetzt, dass die Ampulle, einmal angebrochen, nicht ein zweites Mal benutzt wird. Das Praeparat kann sehr gut Ringerlösung und Glukose ersetzen und infolgedessen kann eine Proteintherapie

auch durchgeführt werden, wenn ein orale Zufuhr unmöglich erscheint oder Schwierigkeiten macht oder wenn Injektionen in Venen, Knochenmark und Abdomen für andere Zwecke aufgespart werden müssen. Es wurde gefunden, dass 20—40 ml pro kg Körpergewicht und Tag in 1—2 Injektionen täglich gegeben, die geeignete Dosis darstellt.

Resumen.

La aminosol-glucosa es un alimento parentérico inocuo cuando se usa subcutáneamente, a condición de que no se use otra vez la ampolla rota. El preparado puede reemplazar muy bien a la solución Ringer y a la glucosa, pudiéndose por consiguiente efectuar una terapia de proteína aunque la alimentación bucal sea difícil o imposible o que las inyecciones en las venas, medula de los huesos o abdomen tengan que reservarse para otros fines. La cantidad adecuada es de 20 a 40 ml por kilo de peso y por día, 1 ó 2 veces diariamente.

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Considérations clinico-psychologiques et thérapeutiques à propos d'un cas d'hémophilie infantile.

Par

M. SCHACHTER.

Les cas d'hémophilie ne semblent pas être fréquents dans notre ville, ni dans notre région. En ce qui nous concerne, sur plusieurs centaines d'enfants vus à nos consultations depuis 1944, par exemple, c'est la première fois qu'il nous est donné d'étudier un petit hémophile, provenant d'une fratrie d'hémophiliques. Mais ce qui a, surtout, déterminé la relation de notre cas c'est moins «le dépistage» — en quelque sorte — d'une nouvelle fratrie d'hémophiliques, que surtout, le fait que nous avons pu : a) étudier (est-ce le premier cas?) le profil rorschachien d'un petit hémophile; b) expérimenter, en quelque sorte, dans ce cas l'intérêt de l'hormonothérapie oestrogène (oestrogènes de synthèse, surtout) préconisée — chez nous — par R. TURPIN et ses collaborateurs, F. BOURLIÈRE et R. SASSIER.

En ce qui concerne le *sondage psychologique profond* des hémophiliques-enfants, le problème qui se posait à nous était le suivant: Peut-on découvrir, à la lumière des méthodes de psychologie projective (type test de RORSCHACH), des éléments indiquant la «participation» consciente du jeune être, aux manifestations engendrées par une affection particulièrement impressionnante, à cause des saignements plus ou moins fréquents qu'elle implique? Cette «participation» est-elle «spécifique» en quelque sorte?

Ce problème de la conscience pathologique (ou encore de la «*Krankheits-Erlebniss*») nous avait déjà préoccupé, lors de l'étude clinico-psychologique de deux petits enfants atteints de mégacolon congénital, et nous avons montré — à cette occasion — qu'en dépit du niveau mental de ces sujets (l'un normal, l'autre un dé-

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bile psychique) les choses se passent comme si les sensations cé-nesthésiques engendrées par les troubles en rapport avec la constipation chronique ou avec les lavements auxquels ils sont soumis, ne franchissent *jamais* un certain niveau, pour devenir une préoccupation consciente ou même semi-consciente. En est-il de même dans notre présente observation concernant une affection plus nettement *psychotraumatisante*?

Quant à la *thérapeutique* de la diathèse, les résultats obtenus, en relativement peu de temps, avec un oestrogène de synthèse, nous retiendront également, en raison de leur intérêt pratique, avant tout.

Analysons, donc, les faits avant de les commenter:

Observation: G. Jean, est âgé de 6 ans lorsque nous le voyons pour la première fois. Il nous est amené, par sa mère, à cause de son mauvais développement physique (il ne pousse plus, dit sa mère) et de l'impossibilité *totale* d'étendre le membre inférieur *droit*, et *relative* pour le membre inférieur *gauche* (cela depuis quelques jours).

Antécédents: dès les premières questions posées concernant le mauvais état et l'impotence des membres inférieurs de l'enfant, nous apprenons les faits importants que voici:

Jean est venu au monde après une fausse couche spontanée (de 40 j) de sa mère. Après lui, une fillette, actuellement âgée de 4 ans 3 mois, est en bonne santé (nous l'avons soumise à un examen très complet et n'avons trouvé rien d'anormal chez elle au double point de vue somatique et psychologique). Après cette fillette, une nouvelle fausse couche spontanée, à 50 j. environ.

La mère, âgée de 36 ans, réglée à 13 ans (menstrues *très* abondantes, mais à rythme régulier; durée 5—6 jours) est également en bonne santé. Nous avons trouvé, chez elle, des incisives supérieures et inférieures (des médianes surtout) assez *suspectes* de syphilis congénitale. Mais l'examen neurologique et oculo-pupillaire est négatif. Plus important à noter est le fait que *son frère* (que nous connaissons également) est un *hémophile* avéré, se soignant depuis de longues années (ankylose et amyotrophie du membre inférieur droit). Dans la famille de ce dernier, notons qu'un *oncle* (frère de sa mère) est atteint d'*hémophilie*, de même qu'un *cousin germain* (toujours maternel) *décédé*, par *hémorragie*, à 30 ans.

Le père de Jean, âgé de 43 ans, est bien portant. Aucune maladie nerveuse ou sanguine. Pas d'éthylisme ou de tabagisme avéré. Prétend ne pas avoir contracté l'infection syphilitique.

Développement de notre petit hémophile: Jean est né à terme, la grossesse et l'accouchement furent normaux. Première dent: 6 mois;

premiers pas: à 9—10 mois; premières paroles: 12—13 mois; propriété sphinctérienne: à environ 12 mois. — Maladies: Jamais de convulsions; coqueluche à 2—3 ans, non compliquée. — Maladie sanguine (hémophilie): le premier «accident» hémophilique se situe à 18 mois; l'enfant est tombé dans l'escalier; il s'est écorché la lèvre, l'arcade sourcilière et la main. Il aurait saigné pendant 4—5 jours, presque sans arrêt! Deux mois plus tard, autre accident qui a frappé le *frenum* de la lèvre supérieure; saignement pendant 5 jours; on l'a cru perdu, aussi fut-il soigné dans un hôpital. — Vers 24 mois, *sans cause précise* (il est difficile de suivre l'enfant tout le temps, précise, avec raison sa mère) on a constaté une enflure des deux genoux, mais à type oscillant; l'enfant souffrait beaucoup et est devenu incapable de faire le moindre mouvement. Durée de cet épisode: environ 7 jours, ensuite régression. Ce symptôme s'est répété, dans les mois suivants, et sous la même forme dramatique. En 1945, à la suite d'une chute, le genou droit aurait été plus touché; l'enflure qui en résulta — très douloureuse — a duré environ 15 jours. En 1946, à cause d'une nouvelle atteinte arthritique de ce genou, on le mit dans un plâtre.

Examen (Mars 1947): L'enfant présente un état d'amaigrissement généralisé (réduction importante des masses adipo-musculaires). Au niveau des membres supérieurs, les articulations sont libres. Nous notons une importante laxité articulaire (doigts et coude), qui existe également chez la mère de Jean. — Aux membres *inférieurs*: peut pratiquement étendre le membre inf. gauche, dont le genou est enflé, chaud. La palpation permet de déplacer, aisément, la rotule; on a la sensation d'une articulation remplie de liquide. Du côté droit, impossibilité de faire le moindre mouvement de flexion ou d'extension du genou.

Circ. médio-fémorale droite: 26, gauche: 27,5 cms.

Circ. jambe au-dessous de la rotule: dr: 19,5 cms; gauche: 20 cms.

Circ. mollet: à droite 17 cms, à gauche 20 cms.

Squelette crânien, normal; circ. 51 cms. Dentition: *normale*, quoique nettement *microdontique*. Gorge, langue: normales. Viscères: normaux. Thyroïde: non palpable. Sphère génitale: petits testicules dans les bourses, crémasteriens vifs, égaux. Prépuce très long. Système nerveux: rien d'anormal. Pupilles normales et réagissant correctement à la lumière, à l'accommodation et à la convergence. Cheveux blonds; iris bleu-clair.

Il nous apparaît superflu de préciser que le diagnostic d'hémophilie chez Jean a été nettement mis en évidence par les épreuves classiques qui ont montré — dans le service hospitalier où on l'a soigné une fois — *une augmentation anormalement grande du temps de coagulation*, alors que le *temps de saignement* (par piqûre du lobule de l'oreille) est pratiquement *normal* (environ 4 minutes). Cette dernière épreuve répétée par nous, a montré un temps de saignement d'environ 4 minutes 1/2, ce qui est une valeur pratiquement normale.

En somme, notre petit garconnet de 6 ans, présente la plupart des symptômes de l'hémophilie à type *familial*. Effectivement, nous avons vu qu'il n'est pas le seul membre de sa fratrie à en être atteint. Les membres atteints (du côté maternel) sont tous des *mâles* (un sujet en est mort). Sa mère n'a jamais présenté des hémorragies de type hémophilique; cependant, il faut mentionner ses règles très abondantes (certains auteurs ont insisté sur cet élément intéressant: voir la monographie récente de P. E. WEIL (1945). Sa sœur, âgée de 4 ans 3 mois, n'a jamais encore présenté des hémorragies. — De plus, notre patient n'a fait jusqu'en ce moment que des déterminations articulaires (genoux) de sa diathèse. Jamais d'autres localisations importantes, et notamment, jamais de localisations nerveuses.

Enfin, au point de vue hématologique, nous venons de voir qu'il présente les deux stigmates fondamentaux de l'hémophilie, à savoir un *retard dans la coagulation sanguine* et un *temps de saignement pratiquement normal*.

Revenant, maintenant aux deux aspects qui nous intéressent, tout particulièrement, chez notre petit malade, voyons ce que nous avons constaté.

En ce qui concerne le *profil psychologique*, sa mère nous avait déjà dit que son enfant est intelligent mais nerveux, méchant parfois; qu'il fait ses devoirs scolaires (à la maison bien entendu) de façon très satisfaisante. Il aime faire des dessins ou des découpages divers. Durant notre examen, la coopération de cet enfant est excellente.

Il accepte le test de RORSCHACH avec un vif intérêt et nous donne 37 réponses. Aucun refus; aucune planche n'a été retournée. Nous servant de la nomenclature symbolique *française* (de M^{me} M. LOOSLI-USTERI), nous résumons, comme suit, le résultat obtenu:

| | | | | | |
|----|----|-------|----|--------------|---------------|
| G | 0 | sF | 31 | An et An. d. | 22, soit 59 % |
| D | 23 | F % | 80 | Obj. | 5 |
| Dd | 10 | CF | 3 | H et Hd | 4, soit 11 % |
| Do | 4 | FC | 2 | Bot. | 2 |
| | | FClob | 1 | Taches | 2 |
| | | | | Nuages | 2 |

Type de perception: *D-Dd-Do*.

Succession: assez raide.

Type de réaction: O K/3 CF + 2 FC, soit 0/4, extra-tensivité égocentrique.

Remarques.

Sans insister ici — cela sort du cadre du présent travail — sur la difficultés des critères de jugement d'un Rorschach chez les enfants d'âge pré-scolaire, et conformément aux vues soutenues, récemment encore par M. FORD (1946), dont l'expérience en la matière est incontestable, nous avons été assez larges avec l'interprétation des résultats données par notre sujet. Il résulte, de ce protocole, que nous avons à faire, effectivement, à un enfant intelligent (F % 80) en dépit de l'absence des G (se rappeler que nous sommes à l'âge de 6 ans, où les globalisations ne sont pas vues chez *tous* les enfants) des K (cela est moins fréquemment le cas) et des réponses vraiment originales. Il est également remarquable de constater que sur 37 réponses, *une seule*, à la pl. VIII a été créditée comme étant Vulg. classique (l'enfant dit: «un petit chien qui s'accroche au parapluie»; il s'agit-là d'une bonne configuration: DF + An et Obj.).

Mais ce qui nous importe le plus, c'est *l'absence* de toute interprétation auto-somatique (c'est à dire, *absence de toute Anat. ou Sang*). Or, étant données les nombreuses chutes avec des saignements prolongés, on aurait pu s'attendre à ce que le petit Jean «donne» du sang, aux planches II et III, et même quelques reminiscences de ce genre à la pl. VIII (médián-bas). Aucune interprétation de ce genre ne fut donnée. Les 3 CF ou FC, se rapportent à des «formes» qu'il voit colorées: ce sont «des choses rouges», des rubans rouges, des arbres verts, des feuilles vertes». Ainsi, ces interprétations constituent son type d'extra-tensivité egocentrique, qui n'a rien d'étonnant chez un enfant qui semble ne pas être pathologiquement (c'est à dire douloureusement) conscient de la maladie dont il est atteint.

Nous précisons ici, que sur 20 profils rorschachiens personnels, concernant des enfants de *moins de 8 ans* révolus, *aucun* n'a donné des interprétations autosomatiques, c'est à dire *Anat.* Ceci est important à souligner.

Par conséquent, comme chez nos deux petits enfants (aussi de moins de 8 ans) atteints de mégacolon congénital, notre petit

hémophilique ne présente au test de RORSCHACH, aucun élément permettant de dire qu'il est, en quelque sorte, conscient (pré-occupé) de sa maladie. Les saignements dont il est la victime ont, en quelque sorte *glissé* sur sa petite personnalité, *sans la toucher encore*. *C'est ce fait que nous voulions bien mettre en évidence.*

En ce qui concerne la *thérapeutique* appliquée, cet enfant avait été soigné, pendant des mois entiers, avec des préparations calciques, de l'hémostyl, anthéma, vitamine K (?) et des injections de *cérum* lors des accidents. Les résultats étaient *assez peu satisfaisants*. L'enfant était presque continuellement alité, impotent. Il fut amené chez nous dans les bras de sa mère, qui nous demandait de faire, si possible, *autre chose*.

Notre attitude thérapeutique fut la suivante: nous avons autorisé la mère de faire 2—3 fois par jour, des massages (au talc) légers des masses musculaires des membres inférieurs (et supérieurs), de mobiliser lentement mais, sans crainte, les articulations des m. inférieurs. Quant à la diathèse hémophilique, nous basant sur les recherches récentes de R. TURPIN et ses collaborateurs F. BOURLIÈRE et R. SASSIER, démontrant l'efficacité nette des oestrogènes (surtout ceux de synthèse, comme dioxy-diéthylstilbène, ou stilboestrol — chez nous standardisé sous le nom de distilbène) qui raccourcissent en peu de jours (parfois en 5—6 jours!) le temps de coagulation sanguine, nous avons prescrit — selon le conseil que recommande R. TURPIN, lui-même — 15 mgr. de distilbène, en trois doses, par semaine et par voie buccale.

Notre attitude thérapeutique — massages et hormonothérapie oestrogénique synthétique, nous a donné, plus vite que nous n'avons pensé, une satisfaction nette. La mère de l'enfant nous a précisé (dans plusieurs lettres) entre autres: «il faut reconnaître — dit-elle — que les hématomes se résorbent plus vite; au lieu de durer 15 à 20 jours avec des grandes souffrances pour l'enfant, il faut compter maintenant 5 à 8 jours, dont 3 en souffrance (douleurs, probablement).» Bien entendu, l'enfant n'est pas guéri de sa diathèse, mais les hématomes qui surviennent lors des chutes ou traumatismes, durent moins longtemps et font moins souffrir l'enfant. Notons aussi et surtout le fait, que grâce aux massages (qui avaient été interdits par deux autres médecins), l'enfant



Fig. Petite gynécomestie à gauche.

«marche bien, presque sans boîterie», nous dit sa mère. Ce résultat a été obtenu peu de semaines après la première visite.

Nous avons revu l'enfant en Oct. 1947. L'efficacité des oestrogènes se maintient. Nous avons noté alors l'existence, du côté *gauche*, d'une petite *gynécomastie*, fait qui n'a rien d'insolite, comme on le sait, étant en rapport avec le traitement hormonal prescrit. — Nous avons réduit la dose hebdomadaire à 10 mgr. en deux fois, et nous avons appris, depuis, que l'hypertrophie mammaire tend à s'effacer.

Il est évident que devenant plus grand et plus «calme», notre petit hémophilique aura moins d'occasions de tomber et de saigner. Entre temps, le traitement stilbénique prescrit, a *largement amélioré* son état diathésique. Nous nous proposons d'essayer d'agir plus intensément, en prescrivant des stilbènes par la voie parentérale.

Résumé.

Un cas d'hémophilie chez un garçonnet de 6 ans; hémophilie nette, de type familial. Cet enfant nous a été présenté dans un mauvais état, impotent (porté sur les bras de sa mère) en raison d'une incapacité motrice totale à droite et relative à gauche (genoux enflés, par arthrite hémophilique). Au point de vue thérapeutique, des massages et l'administration des hormones de synthèse (stilboestrol) par voie orale, ont amélioré rapidement la situation; l'enfant a commencé à marcher bien; le temps de coagulation sanguine s'est amélioré nettement, car la résorption des hématomes est devenue plus rapide (passant de 15 à 20 jours, à 5—8 jours). — Au point de vue psychologique, l'exploration au test de RORSCHACH, nous a montré que l'enfant se comporte comme s'il n'avait aucune expérience consciente (Krankheits-Erlebniss) de la maladie dont il est affligé.

Summary.

A case of hemophilia in a 6-year old boy — typical hemophilia of the familial type. This child came to us in poor condition, with total motor incapacity in the right leg and relative motor incapacity in the left leg (knees swelled by hemophilic arthritis). From the therapeutic point of view, massage and the oral administration of synthetic hormones (Stilboestrol) brought about a rapid improvement; the child began to walk well; after systematic massage of the limbs blood coagulation time was distinctly improved, for the resorption of the hematomas became more rapid, falling from 15—20 days to 5—8 days. — From the psychological point of view, examination by the Rorschach test showed us that the child behaved as though he had no conscience experience (Krankheits-Erlebniss) of the malady from which he suffered.

Zusammenfassung.

Ein klarer Fall von Haemophilie mit familiärem Typus bei einem 6jährigen Knaben. Das Kind war in sehr schlechtem Zustande und musste infolge einer rechtsseitig totalen, linksseitig

relativen Bewegungsunfähigkeit (die Knie infolge haemophiler Arthritis angeschwollen) getragen werden.

Was die Therapie betrifft haben Massage und Verabreichung von synthetischen Hormonen (Stilboestrol) per os den Zustand rasch gebessert; das Kind begann gut zu gehen; systematische Massage der betreffenden Abschnitte wurde fortgesetzt. Die Gerinnungszeit des Blutes besserte sich deutlich, denn die Resorption von Haematomen ging rascher vor sich (in 5—8 Tagen gegenüber 15—20 Tagen vorher). In psychologischer Hinsicht ergab die Untersuchung mit Rorschach-Test, dass sich das Kind so benahm, als ob es sich keines Krankheitserlebnisses bewusst wäre.

Resumen.

Un caso de hemofilia en un muchacho de 6 años; hemofilia neta, de tipo familiar. Este muchacho nos fué presentado en mal estado, impotente (llevado en brazos de la madre) a causa de una incapacidad motriz total en el lado derecho y relativa en el izquierdo (rodillas hinchadas, por artritis hemofílica). Desde el punto de vista terapéutico, los masajes y la administración de hormonas de síntesis (stilboestrol) por vía bucal le mejoraron rápidamente; el muchacho comenzó a andar bien después de sistemáticos masajes de los segmentos; el tiempo de coagulación sanguínea ha mejorado, ya que la resorción de hematomas se ha acelerado (pasando, de 15 a 20 días, a 5—8 días). — Desde el punto de vista psicológico, la exploración con el test de Rorschach ha mostrado que el niño se comporta como si no tuviera ninguna experiencia consciente de la enfermedad que le aflige.

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Three Fatal Cases of Probable Familial Allergy to Human Milk.

By

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Introduction.

At times a pediatrician is faced with clinical syndromes of a nature which lead him to believe that the infant in question does not tolerate his mother's milk. The idea is so contrary to nature that most physicians will think twice before making the diagnosis. Among the general public, on the other hand, it appears to be a common view that human milk may be bad for the infant, and the argument that «the mother's milk was too strong» is often heard in cases of too early weaning. In China there is a variety of the condition in which this notion can be said to rest on a scientific basis, a condition which will be mentioned below. In Europe, however, one must in the vast majority of such cases assume that it is a question of an erroneous regime or due to hypergalactia or hypogalactia, infection or other conditions with no direct relation to the infant's tolerance of human milk.

Cases in which human milk has a really detrimental effect on an infant do occur, but very seldom. Most text-books of pediatrics do not even mention the possibility and those which do describe the condition as «extremely rare». Reviewing the literature one finds very sparse reports of the condition, but still they serve to show that it is a factor which must be borne in mind, as it may be of vital importance that it is recognized and treated in time.

From an aetiological point of view the reported cases of intolerance to human milk are divisible into 2 groups: (1) Intoxication and (2) allergy.

Re (1). This comprises cases in which the mother's milk is found to contain substances with a directly toxic effect on the infant in the amount usually employed. It is a characteristic feature of this group that the milk is equally harmful to all infants who might drink it.

In this group there is only one factor of real practical importance, i. e. the cases in which the mother has been living on a diet deficient in vitamin B 1 during the pregnancy and period of lactation. The incomplete oxidation of carbohydrates due to this form of avitaminosis will result in the accumulation of a number of intermediate metabolic products in the tissues, also in the breast milk. A few of these products (methyl-glyoxal, pyruvates etc.) have a directly toxic effect on infants. The result is an intoxication usually of an acute course, and in most cases with a fatal outcome. In China where the expectant and lactating mothers often live on a diet almost entirely devoid of vitamin B, this is a disease of some consequence. Formerly it was called «infantile beri-beri», but recently it has more correctly been termed «breast-milk (human milk) intoxication» (FEHLY).

Re (2). Cases of allergy.

These cases may be sub-divided into 2 groups: (a) Allergy to foreign protein, (b) allergy to human protein.

(a) Food allergies are more common in children than adults, presumably because the intestinal mucosa of the child is more permeable to unaltered protein (LEVINE). As a rule sensitization to the specific allergen does not occur until the baby has been weaned and received food containing the allergen in question, but still RATNER has reported a series of cases in which he maintains that the infants developed an allergy to certain foods which the mother had taken in excessive amounts during pregnancy and lactation. He states that he receives support from DONALLY in his interpretation of the cases, i. e. that it is a question of transmission from the maternal blood through the placenta (or possibly the breast-milk) to the child, resulting in early allergization. According to RATNER the foodstuffs in question are — in order of frequency: eggs, cow's milk, wheat, meat, oranges, nuts, bananas, and the symptoms: eczema (in the great majority of cases), vomit-

ing, diarrhoea, urticaria. RATNER advances a particularly convincing argument, viz. the fact that the children have in most cases exhibited a positive cutaneous reaction to the food in question before they ever had received it by mouth.

The phenomenon of early allergy has been observed by a large number of workers, but they are not all agreed that the reason is to be sought in an allergization through the mother's milk. LIP-PARD expresses grave doubts, *int. al.* because he has never succeeded in demonstrating antibodies for cow's milk in the breast-milk of a mother, no matter how much cow's milk she is drinking. This reason combined with the fact that the symptoms of allergy in these cases do not occur until the child has been weaned make it unreasonable to consider the phenomenon to be a hypersensitivity to human milk in the strict sense of the word. In addition, all the cases mentioned have been suffering from allergy to foreign protein which ordinarily does not form a component of human milk.

(b) Actual allergy to human milk, i. e. cases in which one must presume that the infant is allergic to human protein, have also been reported. MACEIN has reported 2 cases of constant vomiting following the breast feedings, cured by 3 respectively 5 desensitizing injections with breast milk. One of the patients later developed eczema. LEVEUF & VIGNES mention an infant who right from birth vomited after every breast feeding and followed a downhill course during the first 5 days of life. Therefore the child was weaned and received formulas of dried milk. The vomiting ceased immediately. When the baby was about the leave the department on the 9th day, a breast feeding was given at the insistent wish of the mother. The result was an anaphylactic shock and death. Autopsy showed no pathological conditions. CHAPTAL has reported a case of anaphylactic shock in the 4th month of life. The baby had always had a tendency to vomiting and therefore weaning was started in the 4th month. A few days later, immediately following a breast feeding, the shock occurred, but it could be relieved. LOMBARDI describes a case of a 10 days old baby suffering from an intractable diarrhoea which grew constantly worse. An immediate cure resulted when all human milk was withheld and sub-

stituted by formulas of dried skimmed milk. MARFAN has observed a number of cases of diarrhoea in breast-fed infants, occurring exclusively in connection with the feedings. He is unable to find any other explanation than allergy to the breast-milk, and advances the hypothesis that the pathogenesis may be different blood groups in mother and child. As a rule the prognosis is favourable, the diarrhoea usually ceasing spontaneously in the 3rd to 4th month without any disturbance in the state of nutrition. In the more severe cases it is recommended to substitute the breast-milk with butter-milk or dried milk.

Several cases of allergy to human milk in the same family do not appear to have been reported earlier.

Writer's Cases:

At the Pediatric Department of the State Hospital in Copenhagen 3 cases of probable allergy to human milk in the same family have been treated in the course of 3 years. The severity of the cases and their tragic course justify a detailed report.

At the present time both parents are 37 years of age and have always been healthy. There is no family history of allergic conditions. The mother's blood group is A₁M.Rh +. The eldest child, a girl, was born in 1938. Up to the age of 4 she suffered from frequent diarrhoeas, but since then she has been healthy.

Case No. 1: ♀ N. K. H., born on Aug. 1, 1944, at term. Blood group not stated. Weight at birth 3 200 g, length 50 cm. Vitamin K administered to the mother. Normal delivery.

Already from birth the stools were frequent and green, occurring after each feeding with great force — sometimes squirting out up to 2 metres — ample, loose, not foul-smelling. She was exclusively breast-fed for the first 10 days, and thereupon received supplemental cow's milk because of hypogalactia. From the 12th day there was profuse and forcible vomiting after feedings. Considerable weight loss. Then exclusively mother's milk for the next 5 days. The vomiting ceased immediately, but the loose and frequent stools persisted. The weight loss continued and the mother therefore tried formulas of dried butter-milk (eledon) as a supplement to the mother's milk. This caused a renewed attack of vomiting and the infant was admitted to the Pediatric Department of the State Hospital on August 29, 1944.

On admission the baby was 4 weeks of age, small, thin, but not actually debilitated. She cried loudly and made an impression of being hungry. Satisfactory turgor. Weight 2 550 g. Physical examination showed nothing abnormal. Temperature 37.2° C.

Hæmoglobin 135 per cent, white blood cells 23 560; otherwise the blood picture was normal. Blood urea 58.8 mg per cent, serum proteins total 8.5 per cent. Serum chloride 120 m. Mol., HCO_3 14.8 m. Mol. Urine: Occasional leucocytes, otherwise normal. Stools: No slime, no blood, no pathogenic bacteria.

Because of these signs of dehydration and acidosis immediate administration of physiologic saline solution with glucose, 5 per cent, and sodium bicarbonate in adequate doses. In addition, distilled water at will. After the course of 24 hours expressed wetnurse milk in increasing quantities. The baby drank avidly and did not vomit, but the watery, green, slimy stools persisted. They were not foul-smelling. From Sept. 2 bismuth, 5 cg 3 times daily, from Sept. 5 10 cg 3 times daily until Sept. 19 when the bismuth was stopped. This had no noticeable effect on the diarrhoea. On Sept. 7 the weight had gone up to 3 000 g. The next days were marked by considerable exacerbation and elevation of temperature, spitting and vomiting which quickly improved after a left-sided otitis was diagnosed on Sept. 13 and treated with paracentesis. During this period the weight had been going down and on Sept. 21 the wetnurse milk was supplemented with eledon formulas, 3 per cent, a total of 85 g. This immediately resulted in vomiting and exacerbation of the stools, so it was stopped and the child again received only expressed wetnurse milk. On Sept. 25 a right-sided otitis was diagnosed. Following paracentesis the stools again looked better.

The condition remained practically unchanged until Oct. 10 when the otitis flared up and the temperature rose to 39.9° C, she had 8—10 watery stools in the 24 hours, her general condition grew considerably worse and mild symptoms of tetany supervened. Following a new paracentesis and administration of calcium, sodium bicarbonate, glucose saline solution, and stimulants she gradually got over the critical condition, but it was not until Nov. 4 that she exhibited distinct signs of improvement. The weight had decreased to 2 500 g, hæmoglobin to 64 per cent. The general condition improved perceptibly after a blood transfusion from the mother. She began to gain weight, but the stools remained unchanged. Dec. 1: Weight 3 050 g. Following bismuth medication the stools grew rather more solid, and the general condition appeared to be improving. On Oct. 14 intracutaneous tests were made with lactalbumin (\div) and lactoglobulin ($++$) (dilution 1: 10 000). On Dec. 5: Rhinopharyngitis accompanied by otitis, elevation of temperature and vomiting. In spite of paracentesis, chemotherapy, parenteral administration of fluid and electrolytes, and stimulants she died on Dec. 8. During the last days there had been hæmorrhagic vomiting and mæna.

Autopsy showed no pathological signs in the central nervous system, heart, lungs, kidneys, pancreas or intestinal tract.

Summary of the Case: A baby girl, aged 1 month, with healthy parents, is admitted to the Department because of loose, green, frequent stools, vomiting and weight loss. The vomiting yields to a diet consisting exclusively of human milk, but the loose stools persist. The condition is complicated by a mild otitis and despite an adequate administration of fluid and electrolytes, chemotherapy and human milk diet the disease drags on and ends fatally after more than 3 months in hospital. Autopsy findings negative.

Case No. 2: ♀, B. K. H., born on Feb. 6, 1946. Weight at birth 2 900 g. Uncomplicated delivery. Vitamin K administered to the mother. Blood group AB.

From birth she received mother's milk 6 times daily and a formula of cow's milk, 50 per cent in the night. From the first day of life loose, green, but not foul-smelling stools 6—7 times daily. No vomiting, but occasional spitting. Gradually she was put on a diet of cow's milk increasing amounts up to 350 g daily (50 per cent). Gained weight and was 3 100 g at 1 month. Around March 10 there was a sudden decrease in the breast-milk supply and the supplement of cow's milk was therefore increased to 500 g daily. In the course of the next 4 days the stools grew more and more frequent and the weight loss amounted to 250 g. The mother therefore resorted to a diet of milk from a Human Milk Centre, 700—900 g daily and physiologic saline solution, 200 g, by mouth. On this diet the stools increased to 16—18 times daily. On March 21 the patient received sodium bicarbonate, 100 g daily instead of saline solution, and, in addition, calcium and bismuth. She drank avidly, did not vomit, but grew more and more restless and was therefore hospitalized on March 24, 1946.

On admission she was 6 weeks of age, pale, whimpering, thin and with a somewhat reduced turgor. Temperature 36.8° C, weight 2 900 g, haemoglobin 84 per cent, HCO_3 8.5 m. Mol., leucocytes 42 200. The urine was found to contain protein and numerous erythrocytes, but apart from that nothing pathological. Physical examination showed nothing abnormal particularly no signs of infection.

The acidosis yielded to administration of fluid and electrolytes, the urine returned to normal, the amount of leucocytes was reduced to 11 800 and the haemoglobin to 80 per cent. The weight rose to 3 020 g in 4 days. There was a temporary improvement in the bowel movements, the stools growing more solid and less frequent, occurring 3—5 times daily. At the outset she was given small amounts of human milk, supplemented with water, saline solution and glucose. Gradually the human milk was increased until it amounted to about 600 g daily on Apr. 3.

Apr. 4, 1946: Marked pityriasis of the scalp, face and armpits.

Simultaneously with the eruption of this exanthema the stools began to increase in number without any demonstrable reason. They were loose, almost watery, green and smelt of human milk. There was neither slime nor blood. In spite of a good appetite and ample nourishment the weight fell to 2 800 g where it remained for several weeks. Attempts were made with skimmed human milk, repeated blood transfusions, rice water, carbo medicinalis, and for a week even with mare's milk (supplemental to the human milk) without the slightest effect on the stools or the weight curve. Towards the end of April there was an inexplicable period of fever attended with a temporary exacerbation of the symptoms increasing acidosis and dehydration. Actually, she never recovered from this condition, in spite of administration of fluid and electrolytes and continued blood transfusions. The temperature remained unstable, the weight followed a downward course, haemoglobin around 120 per cent, HCO_3 around 17 m. Mol.

Human milk was withheld for 6 days and substituted by protein milk, amino acids, and sterile water. This treatment failed to lead to any improvement, so human milk was resorted to once more.

From May 26, 1946 the human milk was supplemented with a concentration of amino acids, 0.4 g at each feeding.

On May 27 the case record states: 'The peristalsis is so rapid that both milk and water are voided almost immediately after the feeding, even before the bottle is empty.'

Following a rapid downhill course the patient died on May 28, 1946.

Autopsy: No signs of cystic fibrosis of the pancreas. In the liver and spleen there were accumulations of a brownish pigment which failed to give reaction to iron. In places the lungs were emphysematous, in other places atelectatic. The remaining organs showed nothing abnormal.

Summary of the Case: A baby girl, aged 6 weeks, a sister of the previous patient, is admitted because she has, right from birth, been having frequent, loose, green stools and has not been thriving in spite of an excellent appetite. During the stay in hospital she exhibits eczema of the scalp and face. It proved impossible to find a form of treatment which could make her thrive, and the disease ended fatally after 2 months in hospital. Autopsy failed to give an explanation of the phenomenon.

Case No. 3: ♂, P. K. H., born on Sept. 15, 1947. Weight at birth 3 150 g. Length 49 cm. Vitamin K to mother and child. Blood group AB. On Sept. 23 the patient was transferred from the Maternity Hospital to the Pediatric Department of the State Hospital for observation.

Received exclusively mother's milk. Weight on admission 3 100 g. Haemoglobin 130 per cent. Cried loudly and appeared to be quite healthy. Physical examination revealed nothing abnormal. Urine normal.

From the 14th day of life the stools became somewhat watery, slightly slimy and frequent (5—6 times daily). Apart from this fact the baby got on quite normally, gained weight steadily, having reached as far as 3 820 g on Oct. 12, 1947. At the mother's wish the baby was discharged on Oct. 12.

At home he continued to thrive. He received his mother's milk, 600 g daily, supplemented with human milk from the Municipal Human Milk Centre, 300 g daily. In 3 weeks he gained weight from 3 820 g to 4 370 g. During the first 2 weeks the stools were comparatively normal, but after that they began to be loose and slimy, and the movements grew more frequent. At the same time the baby developed an extensive eczematous eruption in the face, scalp, behind the ears, in the lines of the neck, on the buttocks and legs. For this reason he was re-admitted on November 5, 1947.

On this second admission the objective examination failed to reveal anything abnormal apart from the eczema. Temperature normal, haemoglobin 62 per cent, leucocytes 21 720, urine normal. Blood smears showed 5 per cent, eosinophile cells, otherwise nothing abnormal. Duodenal juice: Trypsin and amylase in normal amounts.

Following a blood transfusion (85 cc.) the haemoglobin percentage rose to 82. There was a steady increase in weight which was 4 650 g on Nov. 17.

The stools remained loose, green and not foul-smelling and the movements were just as frequent. The stools contained ample fat, but no starch, slime, blood, or pathogenic bacteria. The peristalsis was greatly increased and the stools were ejected with great force. There was, however, no meteorism or any symptoms of gastric colic. On Nov. 17 he ceased to gain weight. From Nov. 25 an attempt was made with amidryl, 1/4 tablet 1 hour before each feeding. This treatment was, however, stopped, as it resulted in vomiting in 2 days. Thereupon the mother's milk was withheld and the baby received expressed wetnurse milk, a total of 960 g daily. This made no difference in the stools. From Nov. 28 an attempt was made with pancreatic enzyme, 1 g 6 times daily, but this treatment was stopped in 2 days as it resulted in loss of appetite, indisposition and spitting after the feedings. The movements increased in frequency and the weight decreased to 4 400 g. For a couple of days he was given intramuscular per corten, 5 mg. This, however, resulted in elevation of temperature, unrest and signs of oedema, and was therefore abandoned. »Passive transfer tests» (PROUSNITZ-KUESTNER test) were made with cow's milk proteins, the mother's milk, other human milk, and eggs. In addition, cutaneous tests using the ordinary foods. PROUSNITZ-KUESTNER's test with whole cow's milk as well as lactoglobulin gave a doubtful reaction, all the others were negative.

On Dec. 1 at last soya flour could be procured and from now on the

patient received a diet completely devoid of animal protein, beginning with «soya milk», at first cautiously, but later in increasing amounts and stronger dilutions, until the diet was sufficient with regard to quality as well as calories. (The soya milk was made from the flour of the soya beans from which the fat had been extracted. To this was added water, sugar, vitamins and olive oil in a manner which made a formula of a composition extremely like cow's milk). The effect must be described as dramatic: The fever subsided, the stools immediately grew solid and formed, and in the course of 3 days the movements decreased to 2 daily, the oedema disappeared, the eczema improved perceptibly, the baby began to gain, and his general condition showed distinct improvement. The stools no longer contained fat.

The steady and even improvement in the condition suddenly ceased on Dec. 14, 1947, after a fortnight's treatment with soya milk. On this day the patient suddenly vomited profusely; he grew lax and debilitated and exhibited a syndrome closely resembling anaphylactic shock. The shock could be relieved by means of blood transfusions, administration of fluid and discontinuation of the soya milk. The weight had been reduced to 4360 g and the stools had again grown loose and the movements frequent.

For a couple of days after this attack he was fed oatmeal gruel, mashed bananas, and received dried, powdered carrot, fluid and electrolytes, later supplemented with concentrated amino acids (aminolin) in quantities corresponding to the body weight. At the same time a desensitization was started with dried butter-milk, 10 per cent (beginning with 1 dram and increased by 1 dram at each feeding). When he started vomiting on Dec. 18 the treatment was changed to amino acids and glucose by intravenous drop. He appeared to tolerate this treatment well. The stools were now again solid, formed, and there was even some tendency to constipation and meteorism which yielded to prostigmine in small doses. On Dec. 22 there was a sudden exacerbation. The temperature rose to 39.5° C and the patient exhibited clinical signs of pulmonary oedema. It was impossible to get him through this serious condition, and he died in the course of three quarters of an hour.

Autopsy was not allowed.

Summary of the Case: A brother of the two patients reported above was admitted for observation at the age of 10 days. Apart from frequent loose, green stools he developed normally up to the age of about 7 weeks. At that juncture he exhibited an extensive eczema and the bowel movements increased in frequency. From the age of 9 weeks there was a change without any demonstrable cause: The movements increased still more in frequency and the weight began to go down. Treatment with amidryl, pancreatic enzyme, percorlen, and substitution of the mother's milk with expressed wetnurse milk was of no effect. When the human milk was replaced by «soya milk» there was a temporary improvement of all

the symptoms, but after a fortnight of soya milk a condition supervened, which presumably is to be interpreted as an anaphylactic shock. The condition could again be improved by continued treatment with amino acids, until he suddenly died with symptoms of pulmonary oedema. Autopsy not allowed.

Discussion.

In view of the striking uniformity apparent in the nature of the symptoms, the time of their onset, the similar course and the familial occurrence, it would appear to be warrantable to presume that all three children have been suffering from the same disease. Possibly the cause of the disease is debatable, but so many features suggest an allergic aetiology that the latter must be considered the most likely one.

The following factors indicate allergy:

(1) The symptoms correspond exactly to those described in the cases of hypersensitiveness to human milk reported by earlier authors (especially MARFAN).

(2) Two of the babies (Cases 2 and 3) also exhibited another allergic symptom, viz. eczema. The eruption of the eczema was attended with an exacerbation of the intestinal symptoms.

(3) A temporary improvement was obtained in Case No. 3 when the treatment was changed to administration of «soya milk» and later to amino acid.

(4) Case No. 3 got an allergic shock against soya after a fortnight's treatment.

It appears to be out of the question that the allergic reaction in these cases could be due to some substance taken in excessive amounts by the mother during pregnancy. This theory found no support in the history and besides there was no improvement after her own milk was replaced by milk from a Human Milk Centre. There is every reason to believe that the allergy did not apply merely to all human milk, but also to cow's milk (and possibly to other forms of animal protein), as Cases 1 and 2 reacted by violent vomiting when given cow's milk (No. 3 never received cow's milk). This is a symptom well known in idiosyncrasy to cow's milk, a condition which is not at all rare. This affords an explanation of

the fact that No. 2 failed to exhibit improvement when human milk was substituted by protein milk and that treatment with amino acid in the same case had no favourable effect, as human milk was given simultaneously. Soya flour contains no animal proteins, only vegetable proteins, and in Scandinavia it is never employed as a food for healthy persons. Therefore, the baby could not have been sensitized to these proteins through the placenta or the mother's milk, and one must therefore beforehand expect a satisfactory result from this treatment, if it was a question of hypersensitiveness to some animal protein. And it did work — for a time.

It was not, however, a surprise that an individual so allergic as this patient should also develop an allergy to soya milk. It is well-known that the soya proteins may be absorbed in an almost unaltered state from a completely normal stomach and intestine (SCHWARZ) with a consequent formation of antibodies and a possibility of allergic reaction. Often such sensitization does not require more than 10—14 days. The sudden reaction of Case 3 after 14 days of soya milk treatment is hardly interpretable as anything but an anaphylactic shock caused by soya protein.

The absence of a marked eosinophilia is not a serious objection to the diagnosis — a number of persons known to be suffering from allergy exhibit a normal amount of eosinophils.

Cases 1 and 2 were submitted to various cutaneous tests of allergy to certain foods. The results were partly doubtful, partly negative. They cannot, however, be attributed with any importance as long as the outcome is negative, as they seldom give a positive reaction during infancy, even in cases diagnosed clinically as undoubted allergy (URBACH).

The chief objection to the diagnosis of allergy in these cases is probably the absence of a family history of allergy.

Is there any other diagnosis which affords a satisfactory explanation of these three cases?

Congenital cystic fibrosis of the pancreas? Familial occurrence and the intestinal symptoms (frequent green stools) might suggest this condition, but it was ruled out even before the results of the post-mortem examinations were known: In the first place the

stools were not voluminous and lacked the abominable stench peculiar to pancreatic fibrosis. In the second place the duodenal juice contained trypsin and amylase, and in the third place there were no pulmonary symptoms.

Infection? This is contradicted by the familial occurrence, the appearance and smell of the stools, the absence of pathogenic bacteria, the normal blood picture, and the improvement following administration of soya milk.

Certain factors of the symptomatology might suggest a congenital insufficiency of the adrenal cortex. This diagnosis did not receive any support from determinations of electrolytes in the blood, but in order to leave no stone unturned, percorten was tried as a link in the treatment of Case 3. The result was not encouraging.

It has been hinted by MARFAN that different blood groups in mother and child may be the cause of these syndromes. In that case it must be a question of factors in the blood unknown so far, as the possible constellations of the blood groups — including the Rhesus groups — are far too common in relation to these extremely rare syndromes.

Considering that the symptoms in the three cases reported above were present to some extent from birth, it is to be presumed that the sensitization to milk proteins has taken place in utero. It is difficult to form an opinion of this process — and one can get no further than hypotheses. Nothing is either known with certainty about the mechanism of the allergic condition in the case of food allergies, but in view of the fact that the dominant symptom of the three cases was a greatly increased peristalsis with frequent, squirting, extremely watery stools without smell, one must presume that the parasympathetic nervous system plays an important rôle.

As far as the treatment is concerned, it must depend on the severity of the symptoms. The mild cases described by MARFAN often require no treatment, perhaps some bismuth, belladonna or calcium carbonate, as they usually recover spontaneously at an age of about 3—4 months. The more serious cases require discontinuation of human milk and probably of milk on the whole.

Our experience with soya milk as a substitute was not encouraging, and it is not unlikely that even with dried milk, evaporated milk, strained meats, or similar denatured proteins with comparatively small allergizing properties, a new allergic reaction will quickly be developed by these patients. The most rational procedure appears to be immediate treatment with preparations of amino acids at the same time as attempts are started at desensitization to that food which one proposes to use, in case there is reason to fear an allergic condition towards this food. It would be a natural thing to try desensitization to cow's milk which is so common a constituent of human food. Experience made with children's idiosyncrasy to cow's milk has, however, proved that such desensitization often fails in extremely allergic children, even when the modern antihistamine preparations are resorted to (FLENSBORG). As a rule it is easier with the denatured proteins (butter-milk preparations, dried milk etc.). In Case 3 a desensitization to eleodon was started, but there was not time enough to increase the doses sufficiently to estimate the result before the baby died. It is a different matter altogether whether one is doing these babies any favour in trying to desensitize them, as individuals with so marked allergic tendencies will probably be faced with a very uncertain future.

Summary.

3 cases of probable congenital, familial allergy to human milk are reported.

The dominant symptom in all cases was frequent, squirting watery stools.

In spite of the most varied forms of treatment, all three cases proved fatal.

Résumé.

3 cas de probable allergie congénitale familiale pour le lait humain. Le symptôme dominant dans tous les cas était de fréquentes selles liquides, jaillissantes. Malgré les formes les plus variées de traitements les trois cas ont été fatals.

Zusammenfassung.

Es werden 3 Fälle von scheinbar kongenitaler familiärer Allergie gegen menschliche Milch berichtet. Das Hauptsymptom in allen diesen Fällen waren zahlreiche spritzende wässrige Stühle. Trotz der ganz verschiedenartigen Behandlung gingen alle drei Fälle tödlich aus.

Resumen.

Se informa sobre 3 casos de alergia, probablemente congénita, a leche humana. El síntoma dominante en todos los casos fué frecuentes deposiciones acuosas a chorro. A pesar de las muy variadas formas de tratamiento todos los casos fueron fatales.

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A Simple Micro-Method for Studying the Retraction of the Blood Clot.

By

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The study of haemorrhagic diseases in children created the necessity of a micro-method for studying the retraction of the blood clot. The method (2), that we hitherto generally used, sometimes gave incorrect readings, as do all methods by which the quantity of expressed serum is measured over the clot in a graduated tube containing a residual clot. These erroneous readings are due to the fact that the clot contracts considerably also in breadth with the consequence that serum along the clot will escape measurement. Such remarks as 'complete retraction after two hours' in the patients' records constitute adequate information, which must however to a certain extent be subjective. Both the lab. assistant and the doctor surely prefer a numeral calculus, especially in pathological cases, provided, of course, that the figures are substantially correct.

Ideal conditions for studying the retraction of the blood clot are given when liberated serum, oozing spontaneously and successively, is collected and measured at timed intervals (3, 7). It is then possible to follow both the course and the degree of retraction. Endeavours to provide a micro-method along these lines have unfortunately hitherto failed. One acceptable solution consists in the removal of the clot from the serum at approximately that moment when complete retraction is assumed, after which the residual serum is measured (1, 6 & 8). This method, however, has two substantial disadvantages, to wit, several readings are necessary to follow the coagulation process and, secondly, the removal

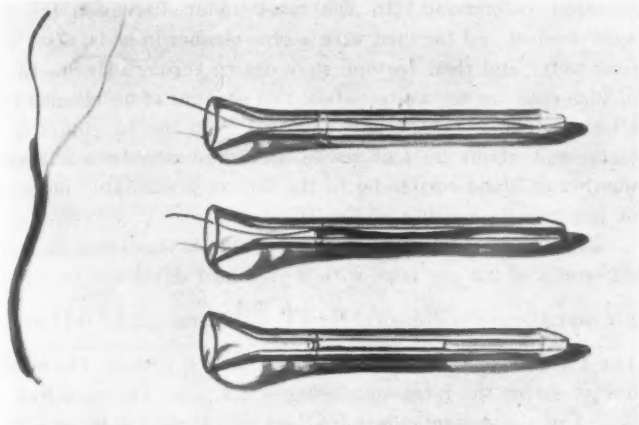
of the clot involves a certain trauma, manifested by the fact that red corpuscles are sometimes torn from the coagulum and appear in large quantities in the serum column. Such tests must then be discarded. If the coagulum is to be removed easily and without injury, it ought preferably to be adherent to a pin or the like, this means admittedly the provision of a coagulation centre, but it will surely be of negligible importance as far as the evaluation of retraction is concerned.

The glass tube used for these tests is 60 mm long and has a uniform inner diameter of 2 mm.¹ To facilitate the inflow of blood specimen, the outer, but not the inner, glass wall of one end of the tube is tapered off, whilst the other end increases conically so that the coagulum might be more easily removed. (Fig. 1). A horse-hair, somewhat longer than the tube, is inserted into the latter until the pointed end is reached. Blood oozing from a finger-prick is then allowed to enter the tube up to a mark 50 mm from the pointed end. Should the collecting of the specimen be unduly troublesome, a smaller quantity, which must then be measured separately, will suffice. The tube is then placed, preferably horizontally, in a Petri-dish that is then put into a damp chamber kept at room temperature. After two hours, and preferably also after twenty-four, the coagulum at both ends of the hair is loosened and the hair with the adherent coagulum drawn out of the tube. The length of the serum column is measured and the percentage of serum expressed from the total quantity of blood is then calculated (with 50 mm blood column = twice the number of mm of serum column).

In order to ascertain the practicability and the sources of error of the method, series of double determinations were made — after 2 hours and after 24 hours — on hospitalized children, who were healthy as far as their blood was concerned.

The method is practical inasmuch as the tubes are easy to fill and the coagulum can be withdrawn in such a manner that the serum column will afterwards display but a small number of red corpuscles, some of which are spontaneously expressed and

¹ The tubes are made after the author's direction by A. B. Rudolph Grave, Malmkillnadsgatan 48 C, Stockholm.

*Fig. 1*

The uppermost tube is unfilled but contains the horse-hair.

The tube underneath is filled with blood, which has completely retracted.

The lowest tube contains expressed serum with a small number of red corpuscles.

To the left there is an extracted hair with adherent coagulum.

visibly deposited already before the removal of the coagulum. For control purposes the tubes of some cases were sealed with plastelina and centrifuged, after which both the corpuscular and the serum columns were measured. The column of blood corpuscles generally measured a couple of millimetres. The methodological error thereby involved is compensated to a certain extent by the fact that some of the serum, corresponding to 1—2 mm was adherent to the wall of the tube above the level of the serum column and increased the length of the corpuscle + serum column after centrifugalization. Test-serum containing a substantial number of corpuscles must be discarded. It is inadvisable to centrifuge such specimens and then to try to correct their values, because the liberated blood corpuscles are presumptive of a trauma that might have influenced the expulsion of the serum.

One condition necessary for the ready release of the coagulum from the wall of the tube is that the latter must be very carefully

cleansed beforehand. In the cases under discussion the tubes were washed and brushed with a pipe-cleaner in suds, after which first water and then acetone were drawn through them. In spite of such care one or two tests failed on account of un-cleaned tubes. Of about 500 cases the hair loosened from the coagulum in four tests, and about 20 had to be discarded due to a substantial number of blood corpuscles in the serum, presumably on account of imperfect cleansing of the tubes.

From 228 double examinations (Table I) there was an average difference of 2.3 per cent with a standard deviation (σ) of ± 4.2 per cent, the methodological error $\left(\frac{\sigma}{\sqrt{2}}\right)$ being $\pm 2.3 \pm 0.11$ per cent.

The average for the retraction was 52.6 ± 0.29 p. c., the standard deviation for the retraction being ± 4.3 p. c. The variation coefficient of the double determinations was thus ± 6.0 per cent. As a variation of this order must be considered permissible in a biological method of this nature, the method seems to be usable. In the calculation of the double determinations the standard deviations of the individual determinations (methodological error) were calculated by the formula $\pm \sqrt{\frac{z d^2}{2 N}}$ (Dahlberg).

The same children were as a rule examined repeatedly at intervals of a few days. The individual variations between the results of the examinations made on the various days — after the elapse of two hours and after twenty-four hours — were calculated and the most irregular series exhibited a distribution range of ± 6.7 per cent, corresponding to a variation coefficient of ± 11.7 per cent (Table II). The average for the variation coefficient was ± 6.2 per cent.

In order to obtain fully comparable values of the clot retraction the latter should be corrected by the use of the hematocrit, either by stating the separated quantity of serum as a percentage of the plasma (ZAHN 9) or by giving the extracorporeal volume (Vol. of clot minus vol. of red corpuscles) (Aggeler et al.). In the present investigation whose foremost purpose was to determine the practical usefulness of the method, no such correction was made.

A comparison between the values obtained after two hours and

Table I.

Review of the double determinations of clot retraction in series from different patients.

The differences are expressed as percentages of expressed serum.

n = number of double determinations

d = difference between the double determinations

σ = standard error of a difference

$\frac{\sigma}{2}$ = standard error of a single determination, error of the method.

| Series | Case J:r N:r | n | $S(d)$ per cent | $S(d)^2$ per cent | σ per cent | $\frac{\sigma}{\sqrt{2}}$ per cent |
|------------------------------|-----------------|-----|--------------------|----------------------|----------------------|---------------------------------------|
| 1 | F 245/47 | 16 | 23 | 53 | ± 1.9 | ± 1.3 |
| 2 | G 287/47 | 14 | 26 | 92 | ± 2.7 | ± 1.9 |
| 3 | F 168/47 | 16 | 54 | 326 | ± 4.7 | ± 3.3 |
| 4 | F 226/47 | 16 | 30 | 74 | ± 2.2 | ± 1.5 |
| 5 | F 222/47 | 15 | 37 | 242 | ± 4.1 | ± 2.9 |
| 6 | F 193/47 | 10 | 22 | 86 | ± 2.9 | ± 2.1 |
| 7 | G 335/47 | 9 | 17 | 53 | ± 2.4 | ± 1.7 |
| 8 | G 337/47 | 10 | 29 | 155 | ± 3.9 | ± 2.8 |
| 9 | G 329/47 | 13 | 36 | 152 | ± 3.4 | ± 2.4 |
| 10 | G 346/47 | 9 | 28 | 158 | ± 4.2 | ± 2.9 |
| 11 | F 290/47 | 10 | 28 | 186 | ± 4.3 | ± 3.1 |
| 12 | F 298/47 | 12 | 34 | 132 | ± 3.3 | ± 2.3 |
| 13 | F 20/47 | 8 | 31 | 176 | ± 4.7 | ± 3.3 |
| 14 | F 304/47 | 11 | 33 | 177 | ± 4.0 | ± 2.8 |
| 15 | G 407/47 | 7 | 11 | 35 | ± 2.2 | ± 1.6 |
| 16 | G 304/47 | 13 | 23 | 75 | ± 2.4 | ± 1.7 |
| 17 | G 297/47 | 12 | 22 | 90 | ± 2.7 | ± 1.9 |
| 18 | Divers samples | | | | | |
| | Examinant 1 | 18 | 28 | 80 | ± 2.1 | ± 1.5 |
| 19 | Divers samples | | | | | |
| | Examinant 2 | 9 | 11 | 37 | ± 2.1 | ± 1.4 |
| Total | | 228 | 523 | 2379 | ± 3.2 | $\pm 2.28 \pm 2.11$ |
| Mean difference 2.3 per cent | | | | | | |

after twenty-four hours was made in 100 cases and the results showed that the 24-hour value was on an average somewhat higher with a difference of 1.10 ± 0.38 per cent. (Calculation according

Table II.

Variations in one and the same patient from one time to another.

| Case | Hgb. per cent | Number of times | Range of the retraction p. c. | Mean per cent | Standard deviation | Variation coeff. p. c. |
|-------------|------------------|--------------------|----------------------------------|------------------|-----------------------|---------------------------|
| 1 | 51—73 | 8 | 50.5—58 | 54.6 | ± 2.7 | ± 4.9 |
| 2 | 78—97 | 7 | 45.5—57 | 50.6 | ± 4.1 | ± 8.1 |
| 3 | 77—84 | 8 | 52—59 | 54.8 | ± 2.3 | ± 4.2 |
| 4 | 77—79 | 8 | 48.5—55.5 | 51.0 | ± 2.6 | ± 5.1 |
| 5 | 74—87 | 8 | 52—58 | 55.3 | ± 2.0 | ± 3.6 |
| 6 | 50—57 | 6 | 52—61.8 | 58.2 | ± 3.3 | ± 5.7 |
| 7 | 96—100 | 5 | 42.5—51 | 46.6 | ± 3.7 | ± 7.9 |
| 8 | 91—98 | 6 | 46.8—52.5 | 50.1 | ± 2.2 | ± 4.4 |
| 9 | 77—88 | 7 | 46.3—53.5 | 51.2 | ± 2.7 | ± 5.3 |
| 10 | 86—88 | 6 | 44.5—54 | 50.9 | ± 3.6 | ± 7.0 |
| 11 | 94—98 | 6 | 47.5—56 | 51.5 | ± 3.0 | ± 5.8 |
| 12 | 77—88 | 6 | 45.8—53.3 | 51.5 | ± 2.9 | ± 5.6 |
| 13 | 76—83 | 4 | 51—59.3 | 54.3 | ± 4.3 | ± 7.9 |
| 14 | 84—92 | 6 | 47.3—56 | 51.5 | ± 3.7 | ± 7.2 |
| 15 | 77—86 | 4 | 51—66.5 | 57 | ± 6.7 | ± 11.7 |
| 16 | 74—75 | 7 | 52—57.8 | 54.6 | ± 2.1 | ± 3.8 |
| 17 | 76—83 | 6 | 41.5—54.3 | 49.7 | ± 4.5 | ± 9.0 |
| Average 6.3 | | | | | | |

to Dahlberg). The difference is however not statistically significant and in normal cases the retraction determined by this method is complete after two-hours.

The retraction process was followed in twelve cases for 30—45 mins., 60 mins., 120 mins., and after 24 hours. Signs of retraction are generally visible already after 30 minutes, and in some cases the serum column could be measured after 45 minutes. It is however difficult to obtain acceptable values prior to complete coagulation because at this stage large numbers of blood corpuscles are inclined to break away from the clot. After 60—90 minutes such measurements could be made in every single case. Values obtained after the elapse of 90 minutes and 120 minutes displayed a difference which was however in some cases negligible, the increase showing an average value of 4.0 ± 0.84 per cent, thus a significant

Table III.

Pathological clot retraction

| Date | Case* | Thrombo- cytes | Time | Clot retraction per cent | | Value 24 hrs.— 2 hrs. |
|-------|-------|-------------------|--------|--------------------------|---------|-----------------------------|
| | | | | Values read | Average | |
| 19.3. | 1 | 154,000 | 2 hrs. | 21, 30 | 25.5 | — 0.5 |
| " | | | 24 " | 20, 30 | 25 | |
| 20.3. | | 96,000 | 2 " | 18, 17 | 17.5 | — 1.5 |
| " | | | 24 " | 16 | — | |
| 18.4. | | — | 2 " | 17, 14, 18 | 16 | + 4 |
| " | | | 24 " | 18, 22 | 20 | |
| 21.4. | | 96,000 | 2 " | 20 | — | +26 |
| " | | | 24 " | 48, 42 | 46 | |
| 24.4. | | — | 2 " | 14, 17 | 15.5 | ± 0 |
| " | | | 24 " | 14, 17 | 15.5 | |
| 29.4. | 2 | 80,000 | 2 " | 12, 12 | 12 | + 8 |
| " | | | 24 " | 24, 16 | 20 | |
| 19.3. | | 84,000 | 2 hrs. | 25, 26 | 25.5 | + 6.5 |
| " | 2 | | 24 " | 40, 24 | 32 | |
| 20.3. | | 120,000 | 2 " | 40, 58, 40 | 46 | + 2 |
| " | | (21.3.) | 24 " | 48 | 48 | |
| 20.4. | 3 | 56,000 | 2 hrs. | 18, 24 | 21 | + 4 |
| " | | | 24 " | 20, 30 | 25 | |
| 29.4. | | 113,000 | 2 " | 55 | — | — 3 |
| " | | | 24 " | 52 | — | |

* Case 1. J:r F 192/47 Leucaemia acuta myeloides. Purpura.

Case 2. J:r G 242/47. Purpura.

Case 3. Stockholm's Isolation Hospital (Epidemisjukhus) J:r 1654/47 Panmyelophthisis.

difference. It therefore seems as if the retraction is normally complete after the elapse of 90—120 minutes.

A series of tests with venous blood drawn from a puncture and squirted immediately into the tubes was made concomitantly with the capillary blood tests. The results obtained coincided both with respect to time and degree of retraction with those of capillary blood.

Pathological Cases.

Four cases with thrombocytopenia were examined for clot retraction. One of the cases, A. W., Journ. F 192/47, a six-year old girl with leukemia acuta myeloides with thrombocytopenia and purpura was examined repeatedly and after two hours a considerably decreased rate of retraction was observable, which in a few cases increased again after 24 hours without however attaining normal values. The tests were easy to read although the results were more differential than in the normal series. See Table II, Case I.

During hospitalization the clinical picture and the blood values of two of the cases showed improvement and the previously diminished degree of retraction became normal again. One of these two cases was a boy with thrombopenic purpura who recovered soon after admittance to hospital. Journ: G 242/47. The other case was from the Isolation Hospital of Stockholm, (Stockholms epidemisjukhus) Journ: 1654/47. A 4-year old girl was hospitalized with a picture of panmyelophthisis with thrombocytopenia. On admittance she had a considerably reduced clot retraction rate but on later improvement of the clinical picture and blood-cytological conditions the clot retraction again became normal. See Table III, Cases 2 and 3.

Case Nr. 4 was from St. Eric's Hospital, Journ: 4035/47. It was a female with chronic myelocytic leukemia with thrombocytopenia and bleeding of the naso-oral mucous membranes (Table IV). In series from 16th Jan. and 17th Jan. she exhibited considerably irregular values although the blood specimen seemed technically to be normal. A new series of blood specimens was taken the same day from two different finger-pricks, the blood being blotted up and the wound dried between the drawing off of every single specimen. The blood was allowed to run spontaneously from one of the finger-pricks whilst it was pressed out of the other, the tubes being numbered chronologically. This time the values were more uniform and there was no tendency to irregularity between the specimens of different chronological number. See Table IV. In order to obtain as homogeneous a series as possible a series of

Table IV.

Pathological clot retraction

Case 4. St. Erik's Hospital, J:r 4035/47. Diagnosis: Chron. myelocytic leukemia with thrombocytopenia.

Review of the differences in series of specimens.

(Bracketed numbers indicate the chronological order of the specimens).

| Date | Thrombo- cytes | Remark at withdrawal | Time | Clot retraction in per cent | |
|----------|-------------------|---|-------|--------------------------------|---------|
| | | | | Values read | Average |
| 16. I. | 36,000 | | 2 hrs | 48, 38, 58 | 48 |
| " | | | 24 " | 52, 42 | 47 |
| 17. I. | — | Proofs from same puncture | 2 " | 50, 54, 36, 32 | 43 |
| " | | Spontaneously drawn from same puncture | 2 " | (1) (2) (3) (4) | |
| " | | | 2 " | 28, 26, 28, 32 | 28.5 |
| " | | Smaller puncture than pre- vious one | 2 " | (1) (2) | |
| " | | 2 is compressed | 2 " | 38, 26 | 32 |
| 20. I. | 51,000 | Venous blood | 3 " | 36, 40 | 38 |
| " | | " " | 24 " | 42, 44 | 43 |
| 30. I. | 65,000 | From same puncture | | (1) (2) (4) (5) | |
| (24. I.) | | 1—3 spontaneously run, | 2 " | 26, 24, 25, 26 | 25 |
| | | 4—5 pressed out | | (3) | |
| | | | 24 " | 48 | |

specimens were taken from venous blood where the effect of external factors during the withdrawal process was practically eliminated. The values obtained were still below normal but now showed only moderate deviations. A chronologically numbered series of specimens taken 10 days later from a finger-prick from which the blood was pressed out into the last two tubes gave considerably reduced 2-hour values which coincided remarkably well.

It would thus seem as if variations in values are greater in pathological cases than in normal patients, probably due to the effect of exogenous factors during the actual withdrawal of the specimen.

Summary.

1. A new simple micromethod for studying the clot retraction is described in which the coagulum is allowed to form around a horse-hair that is withdrawn with the adherent clot, after which the residual expressed serum is measured and the retraction evaluated.

2. 222 double determinations performed on patients with normal blood gave an average difference of 2.3 per cent with a deviation range of ± 3.2 per cent which with an average value 52.6 for the retraction gives a variation coefficient of ± 6.0 per cent for the method.

3. A comparison between the 2-hour and the 24-hour values showed that the latter are on an average somewhat higher, but the difference was not significant.

4. Time studies of the retraction of capillary and venous blood showed that retraction in normal cases is complete after 120 but not after 90 minutes.

5. In four cases of thrombocytopenia the method showed reduced retraction after two hours and as a rule also after 24 hours. The values were more irregular than in the normal series.

I beg to express my gratitude to »Therese and Johan Anderssons minnesfond», for financially supporting the investigation.

My sincere thanks also go to Prof. O. Lindbom, Head of St. Eric's Hospital, Stockholm, as well as to Docent J. Ström and Dr. J. Lindahl, Isolation Hospital of Stockholm, who gave me their kind permission to study cases of pathological clot retraction.

Résumé.

1. Une nouvelle microméthode simple pour l'étude de la rétraction du caillot, dans laquelle on fait coaguler le sang autour d'un crin de cheval que l'on retire avec le caillot adhérent; après quoi le sérum exprimé est mesuré et la rétraction évaluée.

2. 222 déterminations doubles, exécutées sur des patients à sang normal ont donné une différence moyenne de 2,3 % avec un degré de déviation de $\pm 3,2$ % ce qui, avec une valeur moyenne de

52,8 pour la rétraction, donne un coefficient de $\pm 6,0\%$ pour la méthode.

3. Une comparaison entre les valeurs de 2 heures et de 24 heures a montré que les dernières sont en moyenne un peu plus élevées, mais la différence était insignifiante.

4. L'étude de la durée de la rétraction du sang des veines et des capillaires a montré que la rétraction dans les cas normaux est accomplie après 120 minutes, mais non après 90 minutes.

5. Dans 4 cas de thrombocytopénie la méthode a montré une rétraction moindre après 2 heures et généralement aussi après 24 heures; les valeurs étaient plus irrégulières que dans les séries normales.

Zusammenfassung.

1. Es wird eine neue einfache Mikromethode zum Studium der Koagelretraktion beschrieben. Man lässt das Blut um ein Pferdehaar koagulieren, welches mit dem anhaftenden Koagel herausgezogen wird. Dann wird das zurückgebliebene Serum herausgepresst, gemessen und die Koagelretraktion bestimmt.

2. 222 doppelte Bestimmungen wurden bei Patienten mit normalem Blut ausgeführt und ergaben eine Mitteldifferenz von 2,3 % mit einer Fehlmissung von $\pm 3,2\%$, was mit einem Mittelwert von 52,6 für die Retraktion einen Variationskoeffizienten von $\pm 6,0\%$ für die Methode ergibt.

3. Ein Vergleich zwischen 2-Stunden und 24-Stunden-Werten zeigte, dass die letzteren etwas höher waren, der Unterschied aber unbedeutend war.

4. Zeitstudien über die Retraktion von kapillärem und venösem Blut zeigten, dass die Retraktion in normalen Fällen nach 120 Minuten vollständig ist, nicht aber nach 90 Minuten.

5. In 4 Fällen von Trombozythopenie zeigte die Methode eine verminderte Retraktion nach 2 Stunden und als Regel auch nach 24 Stunden. Die Werte waren ungleichmässiger als bei den normalen Serien.

Resumen.

1. Se describe un micrométodo nuevo y sencillo para estudiar la retracción del coágulo, mediante el cual éste puede formarse

alrededor de una cerda de caballo que se retira con el coágulo adherente. Después se mide el residuo de suero exprimido y se avalora la retracción.

2. 222 determinaciones dobles en enfermos con sangre normal dieron una diferencia promedia de 2.3 %, con una magnitud de variación de ± 3.2 %. Esta variación con un valor promedio de 52.6 para la retracción da, utilizando este método, un coeficiente de variación de ± 6.0 %.

3. Una comparación entre los valores de 2 horas y de 24 horas demostró que estos últimos tienen un promedio algo más alto, aunque la diferencia es insignificante.

4. Los estudios de retracción de sangre capilar y sangre venosa demostraron que en casos normales la retracción es completa después de 120 minutos, pero no después de 90 minutos.

5. En 4 casos de trombocitopenia el método mostró retracción reducida después de 2 horas y generalmente también después de 24. Los valores fueron más irregulares que en las series normales.

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La percuti-réaction à la toxine diphtérique concentrée facilitera-t-elle l'épreuve de Schick?

Par

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C'est sous ce titre que nous avons publié une note à la Société Médicale des Hôpitaux de Lyon en 1939, (1) confirmée d'ailleurs par notre thèse de Doctorat en Médecine (2).

Nous avons donc été étonné de lire dans le Compte-Rendu du Congrès International de Pédiatrie de New York l'article du Docteur L. MARYSSAEL de Bruxelles sur «une nouvelle réaction pour la recherche des sujets réceptifs à la diphtérie».

Il ne s'agit pas de mettre en doute la bonne foi de notre collègue belge, car les années de guerre n'ont pas facilité les échanges bibliographiques.

Nous voulons simplement retenir des travaux faits à Bruxelles qu'ils confirment exactement les nôtres et prouvent le grand intérêt de la percuti-réaction dans la prophylaxie de la diphtérie.

La percuti-réaction à la toxine diphtérique a été mise au point en France.

Nous avons été séduit par la simplicité et la sûreté de la percuti-réaction en préconisant cette méthode pour le dépistage de la tuberculose (4) récemment perfectionnée par l'emploi du Timbre Tuberculinique (5).

Cherchant à appliquer l'épreuve au dépistage allergique à d'autres maladies, nous avons montré la valeur de la percuti-réaction dans les Brucelloses (6 et 7) la méthode étant d'application plus facile que l'intra-dermo-réaction à la Mélitine.

Toutefois, l'intérêt d'une épreuve pratique de dépistage nous a surtout paru important dans la prophylaxie de la diphtérie. Nous avons alors proposé la «percuti-réaction à la toxine diphtérique» dont nous nous permettons de rappeler ci-dessous les avantages confirmés par les nouvelles recherches de nos collègues belges.

La supériorité de la percuti-réaction sur l'intra-dermo-réaction classique de Shick et même sur la cuti-réaction de Rey provient de l'antigène d'une part, de la réaction d'autre part:

a) La toxine diphtérique concentrée et glycinée pour percuti-réaction est stable et peut se manipuler sans précaution d'asepsie spéciale, alors que la toxine pure ou diluée a une conservation de quelques jours seulement et doit être manipulée aseptiquement. Il faut, en outre, signaler l'extrême concentration de notre réactif rébelle à toutes injections malencontreuses.

b) On sait que la percuti-réaction est une technique d'exécution simple, bien acceptée des enfants et très facile à interpréter.

La précocité de l'apréuve est à signaler puisque dans certains cas nous avons obtenu des résultats positifs en moins de 24 heures au cours des premiers essais effectués à Lyon, dans le Service du Pr Bernheim.

L'absence de pseudo-réaction, si gênantes dans l'emploi d'un test biologique, est en faveur de la suppression de l'épreuve-témoin.

La percuti-réaction doit rendre de grands services dans la prophylaxie de la diphtérie.

On sait que les épreuves pratiquées au moyen de la toxine diphtérique ont pour but de mettre en évidence l'immunité d'un sujet, les réactions négatives révélant une incontestable résistance à la maladie.

La pratique de la vaccination et de la sérothérapie ne peut que bénéficier de l'emploi d'un test aussi simple que la percuti-réaction.

a) *Vaccination anti-diphtérique et tests d'immunité.* Si les praticiens français ne contrôlent pas plus souvent l'immunité naturelle ou provoquée avant ou après la vaccination anti-diphtérique, c'est qu'ils ne sont pas très familiarisés avec l'intra-dermo-réaction et

qu'il leur est difficile d'avoir toujours à leur disposition les dilutions nécessaires à l'épreuve.

La stabilité de la toxine concentrée et la simplicité de la percuti-réaction doivent permettre de contrôler plus régulièrement l'efficacité de la vaccination anti-diphtérique.

Si l'anatoxine de Ramon s'est imposée dans les Pays Scandinaves ou Anglo-Saxons plus rapidement même qu'en France c'est que l'épreuve de Shick plus habituellement pratiquée permettait un contrôle particulièrement précieux.

b) *Sérothérapie anti-diphtérique et percuti-réaction.* Dans l'entourage des porteurs de germes, il n'est pas indiqué et il semble en tous cas superflu d'injecter du sérum aux sujets présentant des épreuves négatives.

L'emploi d'un test aussi pratique que la percuti-réaction permettrait de dépister rapidement les sujets réfractaires et leur épargnerait une injection de sérum inopportune.

Dans la diphtérie, surtout sa forme bactériologique, il peut être utile de recourir à un test d'immunité.

On sait que Zoeller a montré (8) par la pratique systématique des épreuves de Shick dans les angines diphtériques que le pourcentage de sujets négatifs était très important.

L'extrême précocité de la percuti-réaction rend son emploi possible même dans la diphtérie et chez les sujets négatifs un emploi plus judicieux de la sérothérapie pourrait-être préconisé.

En conclusion, les travaux de notre collègue belge, L. Maryssael ont confirmé nos premières recherches sur la percuti-réaction pour le dépistage de l'immunité anti-diphtérique.

La simplicité d'exécution de cette épreuve, sa facilité et sa précocité de lecture nous incitent à en reprendre l'expérimentation par suite des très grands services qu'elle peut rendre à la prophylaxie de la diphtérie.

Résumé.

En 1939 à deux reprises il a décrit le mode de préparation et d'utilisation de cette toxine diphtérique concentrée après avoir étudié comparativement sur un certain nombre d'enfants l'Intra-

Dermo-Réaction de Schick et la Percuti-Réaction et insisté sur les avantages de cette dernière épreuve.

Summary.

On two different occasions in 1939 the author described a method of preparation and utilization of this concentrated diphtheria toxin, having first made a comparative study of the Schick intradermal reaction and the percutaneous reaction in a certain number of children and come to the conclusion that the latter test was superior.

Zusammenfassung.

1939 wurde in 2 Folgen die Art der Herstellung und Anwendung dieses konzentrierten Diphtherietoxins beschrieben nachdem man bei einer genügenden Anzahl von Kindern vergleichsweise die Intra-Dermo-Reaktion von Schick und die Perkuti-Reaktion studiert und die Vorteile der letzteren für feststehend erachtet hatte.

Resumen.

En 1939 el autor, en dos ocasiones, describió la forma de preparar y utilizar esta toxina diftérica concentrada, después de haber estudiado comparativamente en cierto número de niños la reacción intra-dérmica de Schick y la reacción Percuti e insistido sobre las ventajas de esta última prueba.

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Hypoprothrombinemia in Penicillin Treatment of Acute Infections in Infants.

By

STEN AXTRUP.

Certain substances have a lowering action on the prothrombin content of the blood. The best known of these is dicoumarin. In recent years salicylic acid has also attracted attention in this connection (Govan, Selander, and others). During 1947 the Lund Pediatric Clinic has had 3 cases in which the prothrombin content also showed a fall during treatment with penicillin; 2 of these showed a hemorrhagic tendency at the same time. The cases are briefly reviewed below.

Case 1. ♂ 5 months. (J. 573/1947). Weight at birth: 2.250 gr. Breast fed for 1½ months, then given diluted cow's milk. Became ill 6 days before admission with vomiting and diarrhea which became more and more frequent. Thin. On the day of admission (11/6) the patient was apathetic, with subnormal temperature (35.3 C), much affected condition, thinness (weight 4.4 kg) poor turgor, greyish skin. Cried feebly. Narial respiration. Pharynx slightly reddened. Lungs: moderate number of small, fine, crepitating sounds in the left flank. Thin, spurting, slimy feces.

Therapy. After a diet of tea alone for 24 hours, increasing quantities of breast milk were given. At the same time the patient was given perorally and in the bowel lavage charcoal powder shaken up in water and bismuth and belladonna perorally. On 12/6 there were increasingly clear signs of broncho-pneumonia. Penicillin (Heyden) 10 000 × 8 was begun. During the next few days there was a burn for the worse, with rising temperature, increased dyspnea, and bad colour. The lungs showed many small fine rales bilaterally. On 16/6 the penicillin dose was increased to 30 000 × 8 and on 17/6 sulfathiazole (Astra) was prescribed:

$\frac{1}{4} + \frac{1}{4} + \frac{1}{4}$ gm at 4 hour intervals. On 22/6 the patient's condition was still very bad. He was given 15 ml blood intramuscularly. In the evening blood was oozing from the punctures through which penicillin and blood had been administered earlier. The penicillin was discontinued and the patient given 1 ml K vitamin. On 24/6 he received another 15 ml of blood intramuscularly. On the same day he showed distinct improvement, with falling temperature and improved general condition. He had a number of large bruises across the back and thighs but there was no bleeding from the punctures. The improvement continued rapidly. Weight on discharge 25/7: 5.050 gm. Blood examination: prothrombin on 25/6 73 %, on 26/6 36 %, 11/7 36 %, and 19/7 63 %. At the same time the patient was suffering from anemia, with the lowest values (25/6) as follows: Hb (Sahli) 42 %, red blood cells 2.3 million. After this date the values rose.

Case 2. ♂ 2 months. (J. 623/1947). Weight at birth: 4.170 gm. Mixed diet of equal parts breast milk and citric acid milk (citrido) followed by the latter only. The day before admission the patient began to vomit and was cantankerous and fretful. During the night there was further vomiting. Defecation was normal; there were slight twitches in the right arm. On admission on 28/6 the infant was pale and somewhat affected. Weight: 5.780 gm. The diaper contained loose, somewhat «minced» stools. Pharynx reddened and swollen. Heart, lungs, and abdomen normal. Lumbar puncture: Nonne and Pandey reactions positive. Cells: 13 white and 15 red per visual field. Bisgaard 1 : 25. Temperature subfebrile. After a couple of days the temperature was fluctuating, with peaks up to 39.7 C. The child snuffled and rather harsh respiratory sounds were heard over the right lung (3/7). Penicillin (Heyden) 20 000 \times 8 was commenced. After a few days the temperature was afebrile. On 8/7 the patient seemed restless and pale. The prothrombin value was 17 % but there was no tendency to bleeding. Penicillin was discontinued, and the patient received injections of K vitamin for several days. Prothrombin on 9/7 was 27 %; on 10/7, 44 %; 11/7, 37 %; 14/7, 43 %; and 15/7, 72 %. Patient discharged in good condition on 4/8. Weight 6.410 gm. Other medication: prontosil rubrum (Bayer) 0.3 \times 3 from 2/7—3/7, and sulfathiazole $\frac{1}{4} + \frac{1}{4} + \frac{1}{4}$ gm at 4 hour intervals from 9/7—11/7.

Case 3. ♂ 1 month. (J. 1086/1947). Weight at birth: 2.700 gm. Mixed diet (breast milk and citrido). Transferred from the Maternity Ward to the Pediatric Clinic because he was not gaining weight properly. Weight on admission (29/11) 2.380 gm. Good general condition. Cried lustily, good colour. Internal organs normal. Put on weight well, reaching 2.390 gm on 14/11. On the same day began showing signs of infection (the mother was infected). The patient had distinct thorax retractions, nasal respiration at times, harsh respiratory sounds on the base of the left lung.

and rising temperature. Penicillin was started with a first dose of 5,000 followed by $3\,000 \times 8$. On 15/12 and 16/12 the patient's condition grew worse and worse, with increased difficulty in breathing and crepitating sounds over the left lung. On 16/12 blood was oozing from the injecting pricks. Prothrombin 0 %. Penicillin was discontinued and the patient injected with 2 ml K vitamin. Nevertheless he died on 17/12. The autopsy (obd. J. 551/1947) showed the following. Hemorrhagic diathesis: much blood aspiration, small hemorrhages in serous membranes, and moderate hematoma in the thigh musculature (at the places of injection). Microscopic examination of the lungs showed large regions suffused with blood and fibrin precipitations but no signs of inflammation.

The literature contains reports of hemorrhage as a complication in penicillin treatment. Such phenomena result mainly when the penicillin is applied intrathecally (Erickson, Masten, and Suckle, and others). But similar symptoms have also been noted after subcutaneous or intramuscular injection — though only when the doses were very large (cf. Fleming at the 4th International Microbiological Conference in Copenhagen, summer 1947). It is possible that these hemorrhages may be attributed to a lowering of the prothrombin due to the penicillin. The cases described here all reacted with hypoprothrombinemia, which can naturally not be ascribed with certainty to the penicillin, though it seems highly likely that the drug was responsible. 2 of the cases showed a perceptible hemorrhagic tendency, in 1 case so strong that the hemorrhages were probably instrumental in causing death. The occurrence of this not very common complication of lowered prothrombin content and hemorrhagic tendency can certainly be attributed to the fact that we were here dealing with children treated at an early age, and so not weighing very much. 2 of them, moreover, weighed remarkably little at birth. Hence the penicillin doses were relatively large.

From this we see that it is advisable to observe a certain caution when treating very young infants with penicillin, and particular care should be taken with subjects of this age if salicylic preparations are used simultaneously with the penicillin.

Summary.

3 infants aged 1—5 months reacted to penicillin treatment with hypoprothrombinemia, 2 of them with hemorrhages. In 1 case the bleeding complication was so serious that it probably helped to cause death.

Résumé.

3 enfants âgés de 1—5 mois réagissent au traitement par la penicilline par une manifestation de hypoprothrombinaemia, deux d'entre eux avec hémorragies — l'une si grave que probablement la perte de sang est en partie cause de la mort.

Zusammenfassung.

3 Kinder im Alter von 1—5 Monaten reagierten auf Penicillin-Behandlung mit Hypoprothrombinaemie, zwei von ihnen mit Haemorrhagien, eins so ernst, dass die Blutungs-Komplikation wahrscheinlich mit zur Todesursache beitrug.

Resumen.

3 niños de 1 a 5 meses reaccionaron a tratamiento de penicilina con hipoprotrombinemia: dos con hemorragia y uno de éstos tan seriamente que la complicación de aquélla contribuyó probablemente a ocasionar la muerte.

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FROM THE SURGICAL CLINIC OF THE ACADEMIC HOSPITAL, UPPSALA
(CHIEF: PROFESSOR O. HULTÉN) AND FROM NORRTULL HOSPITAL, STOCK-
HOLM (CHIEF: PROFESSOR A. WALLGREN).

The erythrocyte turnover during the neonatal period.

Experiments with elliptocyte transfusions to newborns.

By

STURE HEDENSTEDT and BO VAHLQUIST.

The radical changes brought about by the transition from intrauterine to extrauterine life also have a marked influence on the blood. With regard to the erythrocytes this is evinced by a reduction of their numbers and a simultaneous replacement of the macrocytes of the fetal stage with normocytes and later with microcytes. Hereby the haemoglobin values fall more sharply than do the erythrocyte figures.

The decrease of the erythrocyte figures and haemoglobin values may be due to an increased destruction of red blood corpuscles and/or a decreased regeneration of new blood corpuscles. Adherents of the haemolytic pathogenesis of icterus neonatorum have advanced various arguments in support of the concept that there is during the first period of life an increased destruction of red blood cells. One of us (B. V.) has earlier critically analysed the validity of these arguments (in the chapter »Die Blutanpassung bei Neugeborenen» pp. 208—225 in the monography *Das Serumeisen*. Acta ped. 28 1941).

In the present study we have endeavoured to illuminate the question of the erythrocyte turnover from a new approach by studying the longevity of red blood corpuscles transfused to newborn infants.

We have in these transfusion experiments used blood from elliptocytics. Hedenstedt (1947) has previously exhaustively treated the methodics and sources of error in this method of determination of the longevity of the erythrocytes.

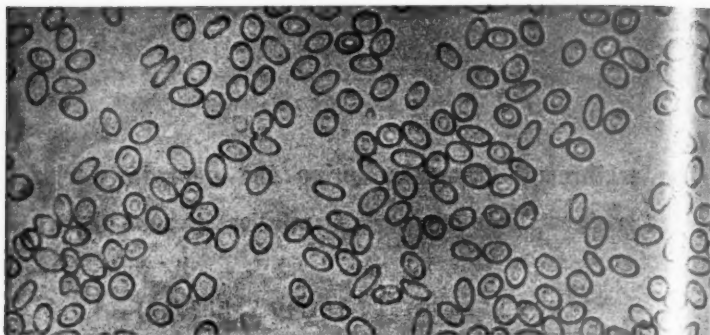


Fig. 1. Red blood corpuscles from an elliptocytic with 27.0 per cent elliptocytes. 500 \times .

Technic and material. Two elliptocytics, one male and one female, served as donors. According to the criteria proposed by Hedenstedt the elliptocytes in both instances comprised roughly 27 % of the total number of erythrocytes. Apart from the elliptocytosis the blood picture was quite normal.

A transfusion from either of these donors was carried out at partus into 8 infants with birth-weights ranging from 2.880 to 4.630 gm. On the average an amount of blood corresponding to 14 cc (8—23 cc) per kg body weight was injected into the umbilical vein. In 5 instances this was done immediately after parturition, in the remaining 3 cases not until the pulsation in the cord had ceased.

In the first two weeks the erythrocyte values of these children experienced a change varying individually from —14 per cent to +17 per cent with an average of —1 per cent. During this time transient hyperbilirubinemia was noted varying from slight to average with a maximal value of 5.6 milligram per cent in a child five days old.

The elliptocyte content was estimated by counts on photographs of wet specimens (cf. fig. 1 and 2), taken immediately before and after the blood transfusion, and also at varying intervals during the following weeks.

In order to obtain comparable values in the different children for the statistical treatment of the material the primary values were corrected with reference to the child's weight, to the amount of blood transfused, and to the elliptocyte content thereof. The values thus obtained have been combined to mean values within different time groups.

Results. The weighed means smoothed with the simple exponential

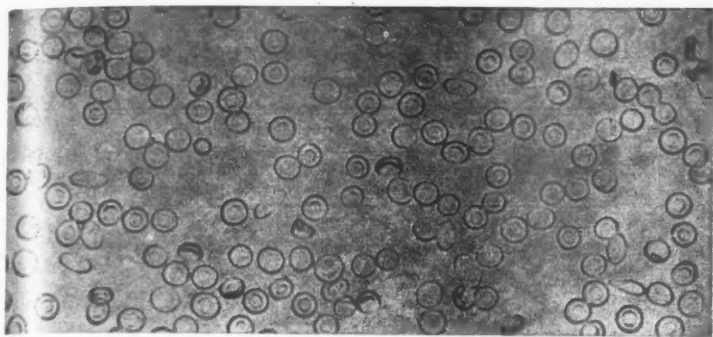


Fig. 2. Red blood corpuscles in a normal subject after intravenous transfusion with the elliptocytic blood seen in fig. 1 (2.3 per cent elliptocytes). 500 \times .

function $C_t = C_0 \cdot e^{-kt}$ by the method of least squares (cf. Hedenstedt) are assembled in table 1.

The smoothed curve thus obtained as well as the observed values on which it is based are presented in fig. 3.

The agreement is better during the first week than on the following weeks which is explicable in consideration of the fact that the elliptocyte content then was higher and the observations more frequent. The smoothing function was in this case $C_t = 11.37 e^{-0.055t}$. The half-life is 12.6 days. During this period of time half of the elliptocytes injected were thus destroyed.

In transfusion experiments with elliptocytic blood on older children the half-life obtained in Hedenstedt's experiments was 13.1 ± 0.9 days. It is from these results obvious that the elliptocytes survive as long in newborns as they do in older children.

Discussion. In speaking of »increased blood destruction» one must explain the interpretation of this expression. If, by way of example, the situation should be that the macrocytic erythrocytes in the fetal stage have a shorter life with a resultant relatively increased daily turnover of erythrocytes and haemoglobin, and this condition continues during the first period of extra-uterine life, it obviously does not motivate the designation »in-

Table 1.

Elliptocyte values at different intervals. The figures in brackets indicate the number of observations.

| Time expressed in days | Elliptocyte values in % | |
|---------------------------|-----------------------------|---------------------------|
| | Observed corrected means | Smoothed weighed means |
| 0.5 | 11.35 (8) | 11.06 |
| 1.5 | 10.58 (8) | 10.46 |
| 2.5 | 10.10 (5) | 9.90 |
| 3.5 | 9.33 (4) | 9.37 |
| 4.5 | 8.77 (6) | 8.87 |
| 5.5 | 8.83 (7) | 8.39 |
| 6.5 | 8.22 (5) | 7.94 |
| 7.5 | 6.10 (2) | 7.51 |
| 8.5 | 7.63 (3) | 7.11 |
| 9.5 | 6.85 (2) | 6.73 |
| 10.5 | 8.10 (1) | 6.37 |
| 12.5 | 4.35 (1) | 5.70 |
| 14.5 | 3.20 (1) | 5.10 |
| 16.5 | 3.45 (1) | 4.57 |
| 17.5 | 3.84 (1) | 4.32 |
| 18.5 | 5.30 (1) | 4.09 |
| 19.5 | 1.90 (1) | 3.87 |

creased destruction of blood». This expression undoubtedly implies the temporary occurrence of a more marked destruction of blood corpuscles than during the period immediately precedent.

An increased destruction of red blood corpuscles may, in principle, be established either a) by the arising of decomposition products in increased amounts, or b) by the occurrence of such a sudden fall of the erythrocyte counts and the haemoglobin values as can not be explained by a decreased erythrocyte formation alone.

ad a). Recent investigations show that the destruction of haemoglobin probably is a very complicated chemical process that may follow different patterns. In the destruction of the haem-component bilirubin is not invariably formed (cf. Singer 1945). It must, on the other hand, be taken into account that

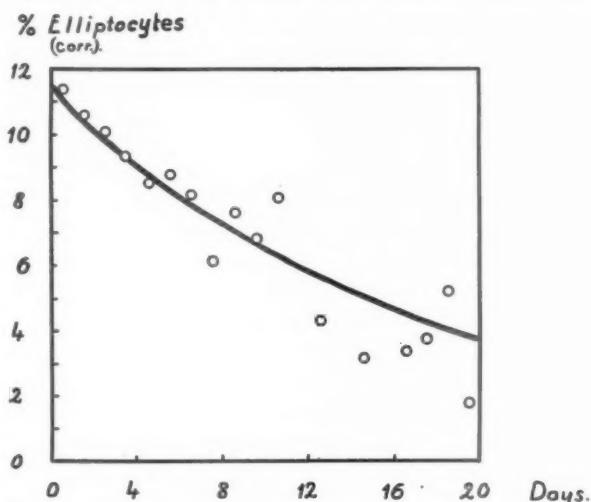


Fig. 3. Decrease in elliptocyte values after transfusion. Weighed means and smoothed exponential curve.

bilirubin may arise also from other substances, thus especially myoglobin. The determination of «haemolytic index» (average pigment output per day \times 100/total haemoglobin in grams) is under such circumstances of limited value.

Irrespective of the difficulties in obtaining reliable values for a «haemolytic index» there is in the newborns the added difficulty that we have no conception whatsoever of the intensity of the rate of destruction of the blood in the period immediately prior to partus. As already pointed out it is impossible to speak of an increased destruction of the blood when we do not know the initial values.

In the destruction of haemoglobin iron also is liberated. The newborn exhibits a hypersideremia with an average serum iron level of roughly 160 γ %. A further analysis reveals (Vahlquist, 1941 p. 171 ff) that these high values merely constitute a continuation of a hypersideremia in the fetal stage. After a temporary sharp fall during the first day of life when the supply of iron from

the mother has ceased and the balance is not as yet restored the values again rise. However this does not prove an increase of the rate of destruction of the blood but merely that the formation of new cells does not keep pace with the destruction of red blood cells.

This is also valid for observations relative to the depots of iron in such organs as the liver and the spleen. These observations prove nothing more than an imbalance between destruction and regeneration. They do not any more than the aforementioned observations provide an answer to the question as to whether or not there is an increased destruction of the blood.

ad b). Earlier investigators noted a considerable decrease of the haemoglobin and erythrocyte values already during the first weeks of life (cf. Goldbloom and Gottlieb, 1929). These results gave rise to the concept of a markedly increased rate of destruction of the blood.

Subsequent investigators have not been able to verify these results. They have found a relatively slow decrease (Faxen, 1935, Waugh et al., 1939).

The circumstance that the normal (concentration-) values for erythrocytes and haemoglobin do not show very marked changes does not, however, exclude that such changes nevertheless may occur. The essential is obviously the behaviour of the total content of erythrocytes and haemoglobin, and hereby consideration must also be given to the blood volume.

An earlier investigation by Lucas and Dearing (1921) gave the result that the blood volume expressed in percentages of the body weight was rapidly reduced during the first period of life. Robinow and Hamilton (1941) were not able to confirm this observation.

The above mentioned investigations were based on a plasma-volume determination in which the amount of whole blood and the total haemoglobin content were calculated indirectly by means of the haematocrit values. This is always very difficult as is clearly demonstrated in an investigation by Meneely et al. (1947). These workers in many cases found a considerable discrepancy between the haemoglobin content measured directly

by means of isotopes and those indirectly calculated by means of the plasma volume and haematocrit values.

The indirect determination of the haemoglobin content is especially difficult in newborns. The divergencies in the erythrocyte distribution in different vascular areas is in infants appreciable already in a comparison between venous blood and blood from skin pricks. This fact was already observed by Haden and Neff (1924).

One of us (Vahlquist 1941 p. 218 ff.) has in detail studied this relationship. At partus the «capillary blood» on the average shows values 10 % higher than venous blood, the difference in occasional cases arising even to 20 %. The difference is gradually smoothed out during the two first weeks of life.

In summary, it must be considered that the present incomplete reports on the behaviour of the erythrocyte and the haemoglobin content during the first weeks of life do not compel us to assume an increased destruction of the erythrocytes. The explanation might as well be a decrease in blood production in combination with a transition from the macrocytic to the normocytic or microcytic type of red blood corpuscles. This will also hold true in the event that recent observations indicating a considerably longer life-time in the erythrocytes than was earlier assumed are proved to be correct.

It seems quite natural that the regeneration of the red blood corpuscles changes after parturition. We know that hypoxemia is perhaps the most important stimulus of an increased activity of the bone marrow. We further know that there in utero is a considerable hypoxemia, which is raised after partus when pulmonary respiration is established.

There is direct support for the assumption that the regeneration of erythrocytes is reduced immediately following parturition. The reticulocyte values fall from an average of 2 to 3 % to less than 0.5 % within less than 1 week (cf. Faxén, 1937). The bone marrow shows a speedy reduction of the number of erythroblasts (Shapiro and Bassen, 1941).

If, however, there temporarily should occur during the neonatal period more or less regularly an increased destruction of

the blood, one must assume the influence of haemolysing factors that exert an exogenous effect on the red corpuscles. These factors should be expected also to influence the foreign corpuscles introduced by transfusion. In acquired haemolytic anemias it has been possible to demonstrate a considerably shorter life-time in the transfused normocytes (Loutit, 1946).

The technic used in our studies on newborns with elliptocytic transfusions gives a lower value for the longevity of the erythrocytes than that obtained by various other methods (differential agglutination, isotope studies). The soundness of our conclusions is not influenced by the factor of the one or the other technique giving the most correct absolute values, as there is in our experiments only a question of a comparison between different age groups investigated with the same technic.

Our investigations clearly show that the life-time of red blood corpuscles transfused to infants at parturition is in agreement with that observed in older children.

It has in the foregoing on several occasions been pointed out that we do not know whether or not the newborn's own blood corpuscles have the same life-time as those formed later on. With reference to morphologic and chemical structure they are divergent in several respects: the mean volume $115 \mu^3$ as against $85 \mu^3$ of the adult, «fetal-haemoglobin» as against definite haemoglobin, and increased haemolytic tendency as against various mechanical but not osmotic factors. The question of the longevity of the erythrocytes in the newborn is from a theoretical point of view of great interest. Certainly it could be solved by applying the differential agglutination method.

Summary.

The authors have carried out 8 experiments with transfusions of blood from elliptocytics to newborns. The longevity of the erythrocytes transfused is in agreement with that found in transfusion to older children.

Résumé.

L'auteur a fait 8 expériences de transfusions de sang à globules elliptocytiques à des nouveau-nés. La longévité des érythrocytes

transfusés correspond à celle trouvée dans la transfusion à des enfants plus âgés.

Zusammenfassung.

In acht Fällen wurde Blut von Elliptocytenträgern Neugeborenen transfundiert. Es ergab sich, dass die Lebensdauer der Erythrozyten ganz der entsprach wie sie mit derselben Methode bei älteren Kindern beobachtet worden war.

Resumen.

Los autores han realizado 8 experimentos con transfusiones de sangre de eliptociticos a recién nacidos. La longevidad de los errocitos transfundidos está de acuerdo con la que se ha observado en transfusiones a niños de mayor edad.

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Added in proof. — In *Lancet* 1948: 214: 513 Mollison has given a preliminary report of studies on the longevity of the erythrocytes in newborns by means of the differential agglutination technique. According to this author transfused erythrocytes from newborns show an initial tendency to supernormal break down, but later on a normal decline, indicating a mixed cell population. In conformity with our results Mollison too has found a normal survival time for adult erythrocytes transfused to newborns and believes it «most unlikely that there is any mechanism which destroys erythrocytes when their concentration exceeds a certain value; thus theories which speak of »the excess red cells being destroyed« are scarcely tenable».

CASE REPORTS

A Rare Form of Congenital Heart Disease.

By

W. BERGMAN and O. MORALES.

From the Children's Department (Head: G. Lindberg) and the Radiological Department (Head: G. Renck), Norrköping Hospital.

Congenital diseases of the heart belonging to Abbot's Group II — morbus coeruleus — can take surprising forms. We have here the opportunity to demonstrate a case from the Children's Department of Norrköping Hospital, where the patient lived to the age of $5\frac{1}{2}$ months with a congenital vitium consisting of a total atresia of the mitral ostium combined with a patent foramen ovale, a defect of the ventricular septum, a stenosis of the isthmus of aorta, and an open ductus Botelli. Varying degrees of stenosis of the mitral ostium have been described, but no case of total atresia has been found in the available literature.

In this case the patient was a girl born in the Maternity Ward of Norrköping Hospital on April 4, 1947. Mother and child were allowed to leave hospital after a normal period of treatment. During routine examination at the Child Welfare Centre the patient was soon observed to be somewhat dystrophic and to be slightly cyanotic. Heart-disease was suspected, but auscultation revealed nothing pathological. Cyanosis increased gradually and was particularly marked when the patient cried vigorously. Because of this she was sent to the Children's Department of Norrköping Hospital for observation on Sept. 18, 1947. She was then $5\frac{1}{2}$ months old.

Apart from slight dystrophia, cyanosis, and hyperglobulia, nothing of interest was found by the physical examination. As a congenital heart disease was suspected, an X-ray examination of the chest was undertaken. This revealed, as seen in fig. 1, that the shape of the heart strongly suggested situs inversus. However, as an atelectasis could be clearly localized to the middle lobe of the right lung, this conclusion had to be abandoned. Then a large interventricular septal defect with a considerable enlargement of the right heart together with transposition of the large vessels was suspected.

The patient had repeated attacks of cyanosis, and her general condition deteriorated gradually. Four days after being admitted to the



Fig. 1. X-ray pictures of the chest shows the peculiar form of the heart.

hospital she died and further examinations, such as electro-cardiogram, could not be undertaken.

The post-mortem examination of the heart showed a hypertrophied left atrium into which the lung veins flowed in a normal manner. There was no direct connection between the left atrium and the left ventricle. An opening with a width of hardly 2 millimeters, corresponding to the foramen ovale, led to the right atrium. The right atrium opened, through a widened tricuspidal ostium, into the right ventricle. The ventricular septum was almost entirely absent. The right ventricle showed a great hypertrophy, the pulmonary artery issued from the normal place and was connected with the aorta by a patent ductus arteriosus. The aorta showed a moderate isthmus stenosis in the proximity of the patent ductus. The middle lobe of the right lung was totally atelectatic. A microscopic examination of the thorax organs revealed no further pathological changes.

The blood circulation was as follows (diagram fig. 2): The arterial blood from the lungs could leave the left atrium only through the very narrow foramen ovale. Together with the venous blood from the great veins, it passed through the right atrium into the common ventricle,

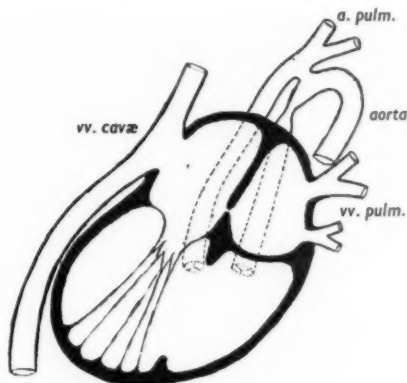


Fig. 2.

whence the mixed blood was distributed between the pulmonary artery and the aorta.

The most interesting point in this case is, therefore, the fact that, in spite of the insignificant amount of arterial blood which passed through the narrow foramen ovale, the patient could live to the age of $5\frac{1}{2}$ months without more marked clinical symptoms.

Summary.

Unusual case of congenital heart disease consisting of a total atresia of the mitral ostium combined with a small interauricular septal defect, a very large interventricular septal defect, a stenosis of the isthmus of aorta, and a patent ductus arteriosus.

Résumé.

Un cas extraordinaire de cardiopathie congénitale consistant en une atrésie mitrale totale combinée à une petite communication interauriculaire, une très grande communication interventriculaire, une sténose de l'isthme de l'aorte et une persistance du canal artériel.

Zusammenfassung.

Ein ungewöhnlicher Fall eines kongenitalen Herzfehlers bestehend aus einer totalen Atrésie des Mitrastostiums kombiniert mit einem kleinen interauriculären Septumdefekt, einem sehr grossen interventrikulären Septumdefekt, einer Stenose des Isthmus Aortae und einem offenen Ductus arteriosus.

Resumen.

Un caso raro de una enfermedad congénita de corazón, que consiste en una atresia total del óstium mitral combinada con un pequeño defecto septal interauricular, un gran defecto septal interventricular, una estenosis del istmo de la aorta y un manifiesto canal arterioso.

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A Case of Vitamin D Resistant Rickets Treated with Massive Doses of Vitamin D₂.

By

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Several authors have described a form of rickets which in its essential features does not differ from the ordinary deficiency form except that it is refractory to vitamin D therapy. The pathogenesis is not understood. In some cases, however, healing has occurred after massive doses of vitamin D. LÜSSY (1946) recently has given a review of the literature on this subject. Up to date only a few cases have been reported and therefore it seems reasonable to give an account of a similar case being treated at the Kronprinsessan Lovisa's Children's Hospital during the last year.

No. 1212/46. F. F., a boy born in August 1942, was first seen at the Children's Hospital in November 1946. His mother is said to have had severe rickets as a child. On account of the bone deformities she was operated upon at the age of about three years. According to a photograph taken shortly after the operation the result was very good. At present, however, she has marked rachitic deformities of the legs and a narrowed pelvis. Her blood phosphorus is greatly lowered (2.8 mg per cent) while the calcium and phosphatase concentrations are within normal limits. The boy is the oldest of three siblings; both of the others are as yet quite well. Delivery was performed through cesarean section.



Fig. 1. F. F. 4 years old.

During the first year of life the patient developed quite normally. He was breast fed during the first 7 months and was under the constant care of a pediatrician. Ever since the age of 2 months he had received vitamin D concentrate as a prophylactic. When he started to walk at the age of 15 months his legs, in spite of this treatment, soon became bowed without any noticeable change of his general health. By means of x-ray rickets was diagnosed and the boy was treated for the following three years with several single massive doses of vitamin D concentrate and with cod liver oil continuously without any noticeable effect.

In November 1946 the boy was admitted to the Children's Hospital. Examination showed a healthy child except for marked signs of rickets: frontal prominences, Harrison's groove, rachitic rosary, epiphyseal enlargements and bowlegs (see Fig. 1). Body length only 91 cm (-14 cm). Body weight 16.5 kg ($+2.8$ kg). Nothing noteworthy from internal organs. Blood pressure 90/60. X-ray examination of the skeleton revealed active rickets. Laboratory data: Blood: Hgb (according to Autenrieth) 92 per cent, red blood corpuscles 4.6 Mill., white cell count

7 600. Erythrocyte sedimentation rate 21 mm. Serum calcium 10.1 (10.5) mg per cent. Blood phosphorus 2.3 (2.5) mg per cent (normal range of variation 4—7 mg per cent). Plasma phosphatase 495 (428) units (normal range of variation 90—310 units). (The figures given represent the values of double determinations.) Serum cholesterol 260 mg per cent. Urine: No albumin, sugar, casts or cells. Stools: macro- and microscopically normal. Renal function tests: Blood non-protein nitrogen 37 (33) mg per cent. Addis count: 88 000 red blood cells. Concentration test and intravenous urography: normal.

12. 1946 the patient received a single dose of 1 000 000 I. U. vitamin D₂ by intramuscular injection. The blood phosphorus then rose to 3.5 (3.5) mg per cent, the plasma phosphatase fell to 265 (270) units and the bone changes showed a certain degree of regress. 20.12. another single dose of 1 000 000 I. U. was given without any noticeable effect as regards the phosphorus and phosphatase levels, while the healing, as shown by the X-ray, continued for some weeks. 14.1.—14.2. 1947 citric acid-sodium citrate treatment was tried without success. Then, according to the experience of among others ALBRIGHT, BUTLER and BLOOMBERG (1937) and LÜSSY (1946) daily doses of 500 000 I. U. vitamin D₂ were given by mouth during a period of ten days (5.2.—13.2.). This massive treatment had a marked curative effect. The blood phosphorus concentration rose to a level between 4 and 5 mg per cent, while plasma phosphatase was lowered from about 300 to c:a 220 units. The serum calcium was slightly raised to about 11.4 mg per cent. No untoward toxic reactions occurred; no calcium salts appeared in the urine. X-ray showed a continuation of the healing process. 13.3.—26.3. another series of 500 000 I. U. daily was given. Neither this time were any toxic reactions found. The boy now was sent home.

Two months later he was again admitted. Meanwhile he had received no treatment. The blood phosphorus concentration still was between 4 and 5 mg per cent and the plasma phosphatase about 210 units. The X-ray changes showed further regress. The patient now received a third series of daily doses of 500 000 I. U. during a period of fourteen days (30.5.—13.6.) without any immediate effect. No toxic reactions were seen. However, crystals of calcium oxalate occasionally appeared in the urine only to disappear when the treatment was omitted. The serum calcium was not raised above normal levels, and no calcium deposits in the kidneys were seen in the X-ray.

During the summer months the boy was staying in the country and he was not re-admitted until five months later. Meanwhile he had received no vitamin D. Yet, the X-ray showed further healing of the rickets. The plasma phosphatase was at the same low level, about 200 units, whereas the blood phosphorus had fallen to 3.2 mg per cent. A new series of daily massive doses of vitamin D₂ was started 10.11. 1947 for a period of ten days.

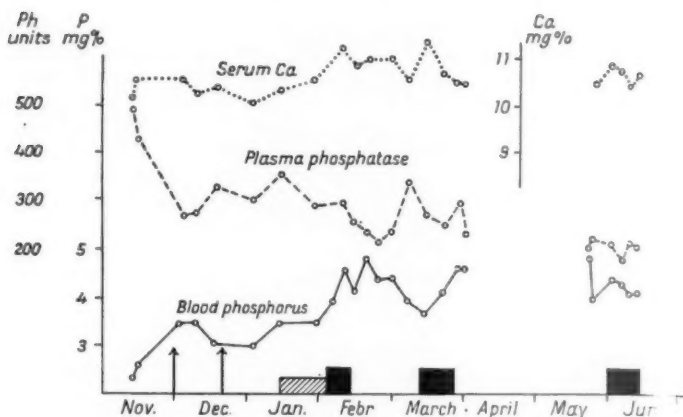


Fig. 2. Diagram showing the levels of serum calcium, blood phosphorus and plasma phosphatase during the period of observation. The arrows represent the single doses of 1 000 000 I. U. vitamin D_2 given intramuscularly, the hatched area the citric acid-sodium citrate medication and the dark areas the periods when daily doses of 500 000 I. U. vitamin D_2 were given by mouth.

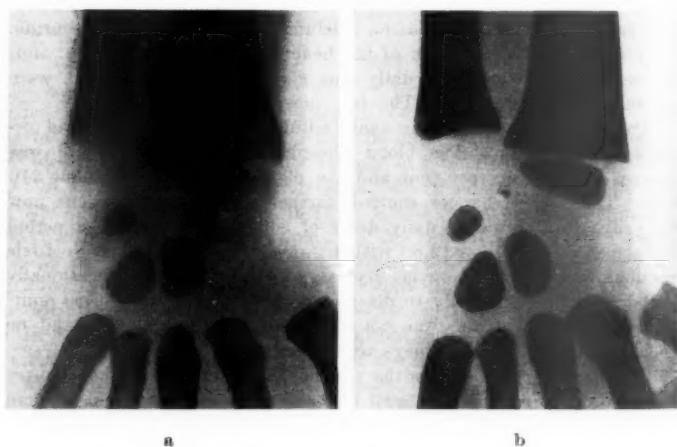


Fig. 3. X-ray of the left wrist (a) 13.11.1946 and (b) 12.6.1947.

At a control examination 31.5. 1948 the X-ray was unchanged and normal values of calcium (11.4, 10.8 mg pr cent), phosphorus (4.16, 4.50 mg per cent) and phosphatase (217, 230 units) were found and a continuation of the treatment was postponed.

10.11. 1948 the boy was again admitted to hospital. The levels of serum calcium, blood phosphorus and plasma phosphatase were still within normal ranges with 10.52 (10.44) mg per cent, 4.40 (4.50) mg per cent and 126 (130) units respectively. The X-ray, however, showed signs of active rickets and a new series of daily doses of 500 000 units vitamin D₂ was started 16.11. 1948.

During the period of observation (2 years) no definite change in body shape has occurred. The rachitic deformities are still as pronounced as previously. He has grown in length only 12 cm.

We have now followed the boy during a period of 1 year. No definite change of his body shape has as yet occurred. The strong bone deformities still remain. However, he has gained in length about 8 cm.

Summary.

A case of rickets resistant to ordinary vitamin D therapy is described. A familial factor has, in all likelihood, played a part in the pathogenesis. Treatment with citric acid-sodium citrate was of no benefit which agrees with the experience of BUTLER. Massive daily doses of vitamin D₂ given by mouth in periods of ten to fourteen days had a marked effect on the blood phosphorus and plasma phosphatase concentrations and brought about a conspicuous healing of the skeletal changes as seen in the X-ray (see Figs 2 and 3). No toxic reactions to these large doses of vitamin D were seen.

Résumé.

Un cas de rachitisme résistant à la thérapie ordinaire par les vitamines D. Un agent familial a probablement joué un rôle dans la pathogénésie. Un traitement par l'acide citrique et le citrate de sodium resta sans résultat, ce qui correspond à l'expérience de Butler. De copieuses doses de vitamines D₂ chaque jour, prises par la bouche, durant des périodes de 10 à 14 jours produisaient un effet remarquable sur le phosphore du sang et sur les concentrations du plasma phosphatase aboutissant à une correction prononcée des changements du squelette, comme le montrent les radiographies no. 2 et 3. On n'a constaté aucune réaction toxique par suite de ces fortes doses de vitamines D.

Zusammenfassung.

Ein gegen die gewöhnliche Vitamin-D-Therapie resistenter Rachitisfall. In der Pathogenese hat wahrscheinlich ein familiärer Faktor eine

Rolle gespielt. Die Behandlung mit Zitronensäure-Natrium Zitrat war ohne Erfolg, was mit der Erfahrung von Butler übereinstimmt. Tägliche sehr grosse Dosen von Vitamin D_2 per os 10—14 Tage lang hatten einen ausgezeichneten Effekt auf den Blutphosphor und die Konzentration der Plasmaphosphatase und bewirkten eine deutliche Besserung der Skelettveränderungen, wie die Röntgenbilder Nr 2 und 3 zeigen. Irgendeine toxische Reaktion auf diese hohen Dosen von Vitamin D wurde nicht beobachtet.

Resumen.

Un caso de raquitis resistente a la terapia corriente de vitaminas D. Probablemente tuvo un factor familiar cierta importancia para la patogénesis. El tratamiento con ácido cítrico-citrato de sodio no dio resultado, lo cual está de acuerdo con las experiencias de Butler. Una diaria dosis maciza de vitaminas D_2 , vía bucal, durante periodos de 10 a 14 días, tuvieron un marcado efecto sobre las concentraciones de fósforo en la sangre y de fosfatasa en el plasma y tuvo como consecuencia una notable curación de las alteraciones esqueléticas, como muestra la radiografía (Figs. 2 y 3). No se observó ninguna reacción tóxica de estas grandes dosis de vitaminas D.

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